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L2 ANSWER 1 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:120425 HCAPLUS
DOCUMENT NUMBER: 134:305011
TITLE: Alpha-1-antitrypsin inhibits human immunodeficiency virus type 1
AUTHOR(S): Shapiro, Leland; Pott, Gregory B.; Ralston, Annemarie H.
CORPORATE SOURCE: Department of Medicine, Division of Infectious Diseases, University of Colorado Health Sciences Center, Denver, CO, 80262, USA
SOURCE: FASEB Journal (2001), 15(1), 115-122
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several observations suggest the existence of potent endogenous suppressors of human immunodeficiency virus type 1 (HIV-1) prodn., and inhibitors of serine proteases may participate in this effect. Alpha-1-antitrypsin (AAT) is the most abundant circulating serine protease inhibitor. Physiol. AAT concns. inhibited HIV-1 prodn. in chronically infected U1 monocytic cells, reduced virus replication in freshly infected peripheral blood mononuclear cells, and blocked infection of permissive HeLa cells. In U1 cells, AAT suppressed activation of the HIV-1-inducing transcription factor NF-.kappa.B. Similar results were obtained using CE-2072, a synthetic inhibitor of host serine proteases. HIV-1 did not replicate in blood obtained from healthy volunteers, but marked replication was obsd. in blood from individuals with hereditary AAT deficiency. These results identify AAT as a candidate circulating HIV-1 inhibitor in vivo. Two different mechanisms of AAT-induced HIV-1 inhibition were identified, including reduced HIV-1 infectivity and blockade of HIV-1 prodn. A novel host-pathogen interaction is suggested, and an alternative strategy to treat HIV-1-related disease may be possible.
IT **208840-22-6**, CE-2072
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(alpha-1-antitrypsin inhibits HIV-1)
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

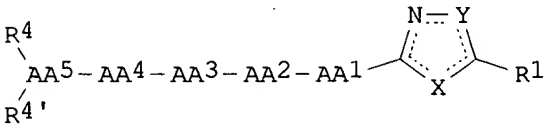
L2 ANSWER 2 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:874195 HCAPLUS
DOCUMENT NUMBER: 134:29708
TITLE: Preparation of .alpha.-keto heterocycles as serine protease inhibitors
INVENTOR(S): Gyorkos, Albert C.; Spruce, Lyle W.; Leimer, Axel H.; Cheronis, John C.
PATENT ASSIGNEE(S): Cortech, Inc., USA
SOURCE: U.S., 36 pp., Cont.-in-part of U.S. 5,807,829.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 18
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6159938 | A | 20001212 | US 1997-859242 | 19970520 |
| US 5618792 | A | 19970408 | US 1994-345820 | 19941121 |
| US 5807829 | A | 19980915 | US 1996-761190 | 19961206 |
| US 6037325 | A | 20000314 | US 1998-69823 | 19980430 |

PRIORITY APPLN. INFO.: US 1994-345820 A2 19941121
US 1996-761190 A2 19961206
US 1996-698575 A1 19960815

OTHER SOURCE(S): MARPAT 134:29708

GI



I

AB Heterocyclyl peptides I [AA1, AA2, AA3, AA4, AA5 are amino acid residues or mimetics or a direct bond; R4, R4' = COR5, CONHR5, SO2R5, CO2R5, CO-(C5-6)aryl-COR5, CH2R5 or R5, where R5 = H, alkyl, alkenyl, (un)substituted alkynyl, cycloalkyl, alkylcycloalkyl, aryl or arylalkyl optionally comprising 1-4 heteroatoms (N, O and S) and optionally substituted, or are absent or R4 and R4' together form a ring comprising 5-7 atoms selected from C, N, S and O; R1 = alkyl or alkenyl optionally substituted with 1-3 halo or hydroxy, alkylamino, cycloalkyl, aryl, etc.; Y, X = O, S, N or substituted N] were prepd. for inhibition of serine protease. Thus, N-acetyl-L-leucyl-N-[(1S)-4-[(aminoiminomethyl)amino]-1-[(5-phenyl-1,3,4-oxadiazol-2-yl)carbonyl]butyl]-L-leucinamide (CQ-0002) was prepd. and inhibited trypsin with ki = 0.62 nM.

IT **208840-22-6P**, Ce-2072
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of .alpha.-keto heterocycles as serine protease inhibitors)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:819473 HCAPLUS
DOCUMENT NUMBER: 134:5159
TITLE: Preparation of tripeptoid analogs as serine protease inhibitors
INVENTOR(S): Gyorkos, Albert C.; Spruce, Lyle W.
PATENT ASSIGNEE(S): Cortech, Inc., USA
SOURCE: U.S., 107 pp., Cont-in-part of U. S. Ser. No. 761,190.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 18
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| US 6150334 | A | 20001121 | US 1997-985201 | 19971204 | |
| US 5618792 | A | 19970408 | US 1994-345820 | 19941121 | |
| US 5807829 | A | 19980915 | US 1996-761190 | 19961206 | |
| WO 9824806 | A2 | 19980611 | WO 1997-US21636 | 19971205 | |
| WO 9824806 | A3 | 19981015 | | | |

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

| | | | | | |
|---|---|---|---|---|---|
| AU 9855894 | A1 | 19980629 | AU 1998-55894 | 19971205 | |
| AU 734615 | B2 | 20010621 | | | |
| EP 954526 | A2 | 19991110 | EP 1997-952232 | 19971205 | |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

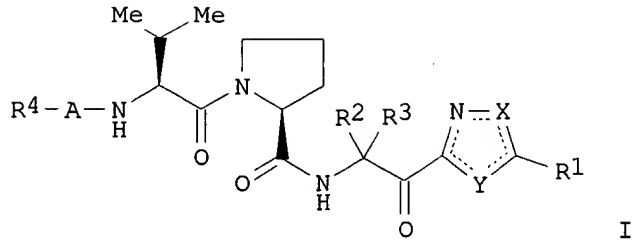
| | | | | | |
|---|---|---|---|---|---|
| CN 1247542 | A | 20000315 | CN 1997-180392 | 19971205 | |
| JP 2001507679 | T2 | 20010612 | JP 1998-525656 | 19971205 | |
| JP 3220169 | B2 | 20011022 | | | |
| JP 2001192398 | A2 | 20010717 | JP 2000-197432 | 19971205 | |
| US 6037325 | A | 20000314 | US 1998-69823 | 19980430 | |
| US 6001813 | A | 19991214 | US 1998-90046 | 19980603 | |
| NO 9902734 | A | 19990802 | NO 1999-2734 | 19990604 | |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1994-345820 | A2 | 19941121 |
| US 1996-761190 | A2 | 19961206 |
| US 1996-698575 | A1 | 19960815 |
| US 1996-760916 | A | 19961206 |
| US 1996-761313 | A | 19961206 |
| US 1996-762381 | A | 19961206 |
| US 1996-771317 | A | 19961206 |
| US 1997-984881 | A | 19971204 |
| US 1997-984884 | A | 19971204 |
| US 1997-985056 | A | 19971204 |
| US 1997-985201 | A | 19971204 |
| US 1997-985298 | A | 19971204 |
| JP 1998-525656 | A3 | 19971205 |
| WO 1997-US21636 | W | 19971205 |

OTHER SOURCE(S): MARPAT 134:5159

GI



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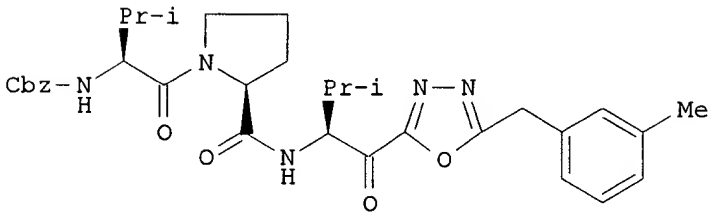


II

AB Tripeptides I [X, Y = O, N, or S, provided that at least one of X or Y = N; R1 = (un)substituted (C5-12)aryl, (C5-12)arylalkyl, (C5-12)arylalkenyl, fused (C5-12)aryl-cycloalkyl, alkyl- or alkenyl-fused (C5-12)aryl-cycloalkyl optionally comprising one or more heteroatoms selected from N, S, or non-peroxide O; R2, R3 = H or alkyl; A = CO, NHCO, SO2, O2C, or CH2; R4 = H, alkyl, alkenyl, cycloalkyl, aryl, or arylalkyl (with provisos)] were prepd. as serine protease inhibitors, including inhibitors of human neutrophil elastase. Thus, peptide I (Cbz = benzyloxycarbonyl) (CE-2072) was prepd. and showed Ki = 0.025 nM for inhibition of elastase.

IT **208840-22-6P**, CE 2072
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of tripeptoid analogs as serine protease inhibitors)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:628160 HCAPLUS
DOCUMENT NUMBER: 133:232870
TITLE: Inhibitors of serine protease activity, and methods and compositions for treatment of viral infections and other conditions
INVENTOR(S): Shapiro, Leland
PATENT ASSIGNEE(S): The Trustees of University Technology Corp., USA
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000052034 | A2 | 20000908 | WO 2000-US5558 | 20000303 |
| WO 2000052034 | A3 | 20010111 | | |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-123167P P 19990305
US 1999-137795P P 19990603

OTHER SOURCE(S): MARPAT 133:232870

AB A method of treating and preventing viral infection is provided. In particular, a method of blocking viral infection facilitated by a serine proteolytic activity is disclosed, which consists of administering to a subject suffering or about to suffer from viral infection a therapeutically effective amt. of a compd. having a serine protease inhibitory or serpin activity. Among compds. are .alpha.1-antitrypsin (AAT), peptide derivs. from the carboxyterminal end of AAT, and man-made, synthetic compds. mimicking the action of such compds. The preferred viral infections include retroviral infection such as human immunodeficiency virus (HIV) infection. A method for treating other pathol. conditions mediated my a serine protease is also disclosed.

IT **208840-22-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors for treatment of viral infections and other conditions, and use with other agents)

L2 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:628010 HCAPLUS
DOCUMENT NUMBER: 133:217681
TITLE: Inhibitors of serine protease activity, and methods and compositions for treatment of herpes virus infections
INVENTOR(S): Shapiro, Leland
PATENT ASSIGNEE(S): The Trustees of University Technology Corporation, USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000051625 | A1 | 20000908 | WO 2000-US5557 | 20000303 |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG,

KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1999-123167P P 19990305
US 1999-153942P P 19990915
OTHER SOURCE(S): MARPAT 133:217681
AB Compns. and methods of treating and preventing a viral infection are provided. A method of blocking a viral infection facilitated by a serine proteolytic (SP) activity is disclosed, which involves administering to a subject suffering or about to suffer from a viral infection a therapeutically effective amt. of a substance having serine protease inhibitory activity or serpin activity. Among the substances found to be useful are .alpha.1-antitrypsin (AAT), peptide derivs. from the carboxy terminal end of AAT and synthetic drugs mimicking the action of such substances. The invention is particularly well suited for checking a viral infection mediated by members of herpesviridae family.
IT **208840-22-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:628009 HCAPLUS
DOCUMENT NUMBER: 133:217725
TITLE: Methods and compositions using serine protease inhibitors useful in inhibiting apoptosis, and therapeutic use thereof
INVENTOR(S): Shapiro, Leland
PATENT ASSIGNEE(S): The Trustees of University Technology Corporation, USA
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000051624 | A2 | 20000908 | WO 2000-US6069 | 20000303 |
| WO 2000051624 | A3 | 20001228 | | |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1999-123167P P 19990305
AB A method is provided for treating an animal suffering a disease characterized by excessive apoptosis by administering a therapeutically effective amt. of at least one serine protease inhibitor and thereafter

monitoring a decrease in apoptosis. The inhibitor of the invention includes .alpha.1-antitrypsin or an .alpha.1-antitrypsin-like agent, including but not limited to oxidn.-resistant variants of .alpha.1-antitrypsin, and peptoids with antitrypsin activity. The diseases treatable by the invention include cancer, autoimmune disease, sepsis neurodegenerative disease, myocardial infarction, stroke, ischemia-reperfusion injury, toxin induced liver injury and AIDS. The method of the invention is also suitable for the prevention or amelioration of diseases characterized by excessive apoptosis.

IT **208840-22-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors for inhibiting apoptosis, and therapeutic use)

L2 ANSWER 7 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:628008 HCAPLUS
DOCUMENT NUMBER: 133:217724
TITLE: Inhibitors of serine protease activity, and methods and compositions for treatment of nitric oxide-induced clinical conditions
INVENTOR(S): Shapiro, Leland
PATENT ASSIGNEE(S): The Trustees of University Technology Corp., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000051623 | A2 | 20000908 | WO 2000-US5556 | 20000303 |
| WO 2000051623 | A3 | 20001214 | | |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6489308 | B1 | 20021203 | US 2000-518097 | 20000303 |

PRIORITY APPLN. INFO.: US 1999-123167P P 19990305
US 1999-156523P P 19990929

AB A method of treating and preventing diseases is provided. In particular, compns. and methods of blocking diseases assocd. with aberrant levels of nitric oxide and facilitated by a serine proteolytic activity are disclosed, which consist of administering to a subject a therapeutically effective amt. of a compd. having a serine protease inhibitory activity. Among effective compds. are .alpha.1-antitrypsin and synthetic drugs mimicking some or all of the actions of .alpha.1-antitrypsin.

IT **208840-22-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(serine protease inhibitors for treatment of NO-induced diseases)

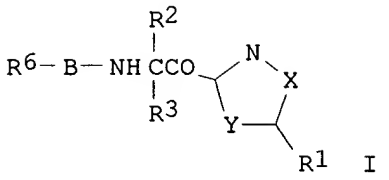
L2 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:47017 HCAPLUS
DOCUMENT NUMBER: 132:78559
TITLE: Preparation of heterocyclic compounds as serine protease inhibitors
INVENTOR(S): Gyorkos, Albert; Spruce, Lyle W.
PATENT ASSIGNEE(S): Cortech Inc., USA
SOURCE: U.S., 107 pp., Cont.-in-part of U.S. 5,891,852.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 18
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6015791 | A | 20000118 | US 1997-984881 | 19971204 |
| US 5618792 | A | 19970408 | US 1994-345820 | 19941121 |
| US 5891852 | A | 19990406 | US 1996-762381 | 19961206 |
| WO 9824806 | A2 | 19980611 | WO 1997-US21636 | 19971205 |
| WO 9824806 | A3 | 19981015 | | |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9855894 | A1 | 19980629 | AU 1998-55894 | 19971205 |
| AU 734615 | B2 | 20010621 | | |
| EP 954526 | A2 | 19991110 | EP 1997-952232 | 19971205 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| CN 1247542 | A | 20000315 | CN 1997-180392 | 19971205 |
| JP 2001507679 | T2 | 20010612 | JP 1998-525656 | 19971205 |
| JP 3220169 | B2 | 20011022 | | |
| JP 2001192398 | A2 | 20010717 | JP 2000-197432 | 19971205 |
| US 6037325 | A | 20000314 | US 1998-69823 | 19980430 |
| NO 9902734 | A | 19990802 | NO 1999-2734 | 19990604 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1994-345820 | A2 | 19941121 |
| US 1996-762381 | A2 | 19961206 |
| US 1996-698575 | A1 | 19960815 |
| US 1996-760916 | A | 19961206 |
| US 1996-761190 | A | 19961206 |
| US 1996-761313 | A | 19961206 |
| US 1996-771317 | A | 19961206 |
| US 1997-984881 | A | 19971204 |
| US 1997-984884 | A | 19971204 |
| US 1997-985056 | A | 19971204 |
| US 1997-985201 | A | 19971204 |
| US 1997-985298 | A | 19971204 |
| JP 1998-525656 | A3 | 19971205 |
| WO 1997-US21636 | W | 19971205 |

OTHER SOURCE(S): MARPAT 132:78559
GI



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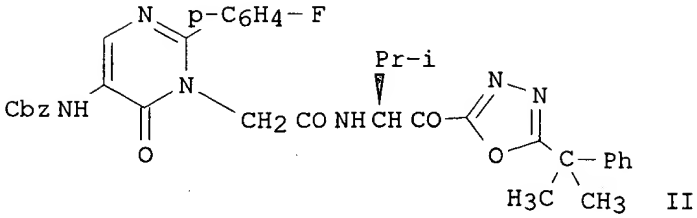

II

AB The present invention relates to a series of compds. of general structure I [ X, Y = O, N, or S provided that at least one of X or Y = N; R1 = C5-12 aryl, C5-12 arylalkyl, or C5-12 arylalkenyl with at least one N, S, and O; R2, R3 = H or alkyl; B = S(O)2 or C(O); R6 = heterocycles (generic structures given)] that are useful as serine protease inhibitors, including inhibitors for human neutrophil elastase. In an in vitro test for inhibition of elastase, the title compd. II shows the Ki value of 78.3. Compds. of the invention are useful in treating conditions such as adult respiratory distress syndrome, septic shock, and multiple organ failure.

IT **208840-22-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclic compds. as serine protease inhibitors)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:794318 HCAPLUS
DOCUMENT NUMBER: 132:23197
TITLE: Preparation of N-substituted prolinyl peptide analogs as serine protease inhibitors
INVENTOR(S): Gyorkos, Albert; Spruce, Lyle W.
PATENT ASSIGNEE(S): Cortech Inc., USA
SOURCE: U.S., 107 pp., Cont.-in-part of U.S. 5,869,455.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 18
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6001811 | A | 19991214 | US 1997-984884 | 19971204 |

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|---|---|---|---|---|---|
| US 5618792 | A | 19970408 | US 1994-345820 | 19941121 | |
| US 5869455 | A | 19990209 | US 1996-761313 | 19961206 | |
| WO 9824806 | A2 | 19980611 | WO 1997-US21636 | 19971205 | |
| WO 9824806 | A3 | 19981015 | | | |

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|---|
| AU 9855894 | A1 | 19980629 | AU 1998-55894 | 19971205 | |
| AU 734615 | B2 | 20010621 | | | |
| EP 954526 | A2 | 19991110 | EP 1997-952232 | 19971205 | |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

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|---|---|---|---|---|---|
| CN 1247542 | A | 20000315 | CN 1997-180392 | 19971205 | |
| JP 2001507679 | T2 | 20010612 | JP 1998-525656 | 19971205 | |
| JP 3220169 | B2 | 20011022 | | | |
| US 6037325 | A | 20000314 | US 1998-69823 | 19980430 | |
| NO 9902734 | A | 19990802 | NO 1999-2734 | 19990604 | |

PRIORITY APPLN. INFO.:

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|---|---|---|
| US 1994-345820 | A2 | 19941121 |
| US 1996-761313 | A2 | 19961206 |
| US 1996-698575 | A1 | 19960815 |
| US 1996-760916 | A | 19961206 |
| US 1996-761190 | A | 19961206 |
| US 1996-762381 | A | 19961206 |
| US 1996-771317 | A | 19961206 |
| US 1997-984881 | A | 19971204 |
| US 1997-984884 | A | 19971204 |
| US 1997-985056 | A | 19971204 |
| US 1997-985201 | A | 19971204 |
| US 1997-985298 | A | 19971204 |
| WO 1997-US21636 | W | 19971205 |

OTHER SOURCE(S): MARPAT 132:23197


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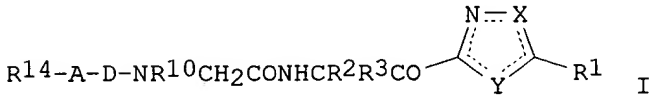


I


AB Proline analogs I [X, Y = O, S, N or substituted N; R1 = (un)substituted alkyl, alkenyl, or alkynyl, hydroxy, amino, alkylamino, dialkylamino, cycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, cycloalkenyl, alkylcycloalkenyl, alkenylcycloalkenyl, aryl, arylalkyl, arylalkenyl, etc.; R2, R3 = H, (un)substituted alkyl or alkenyl, -RCOR', -RCO2R', -RNR'R''R0, or -RCONR'R'', where R is alkyl or alkenyl and R', R'', and R0 are H, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl, etc.; R10 = aryl, arylalkyl, arylalkenyl, cycloalkyl, alkylcycloalkyl, etc.; D is a direct bond or an amino acid selected from proline, isoleucine, cyclohexylalanine, or cysteine optionally substituted at sulfur, A is a direct bond, CO, NHCO, SO2, OCO, CH2; R14 = H, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, alkylcycloalkyl, etc.] were prepd. as serine

protease inhibitors. Thus, (benzyloxycarbonyl)-L-valyl-N-[1(S)-[[5-(3-methylbenzyl)-1,3,5-oxadiazolyl]carbonyl]-2-methylpropyl]-L-prolinamide was prepd. and showed Ki = 0.025 nM for inhibition of human neutrophil elastase.

IT **208840-22-6P**, CE 2072
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of prolinyl peptide analogs as serine protease inhibitors)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:779215 HCAPLUS
DOCUMENT NUMBER: 132:36032
TITLE: Preparation of prolinyl peptide analogs as serine protease inhibitors
INVENTOR(S): Gyorkos, Albert; Spruce, Lyle W.
PATENT ASSIGNEE(S): Cortech Inc., USA
SOURCE: U.S., 110 pp., Cont.-in-part of U.S. 5,801,148.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 18
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5998379 | A | 19991207 | US 1997-985056 | 19971204 |
| US 5618792 | A | 19970408 | US 1994-345820 | 19941121 |
| US 5801148 | A | 19980901 | US 1996-771317 | 19961206 |
| WO 9824806 | A2 | 19980611 | WO 1997-US21636 | 19971205 |
| WO 9824806 | A3 | 19981015 | | |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9855894 | A1 | 19980629 | AU 1998-55894 | 19971205 |
| AU 734615 | B2 | 20010621 | | |
| EP 954526 | A2 | 19991110 | EP 1997-952232 | 19971205 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| CN 1247542 | A | 20000315 | CN 1997-180392 | 19971205 |
| JP 2001507679 | T2 | 20010612 | JP 1998-525656 | 19971205 |
| JP 3220169 | B2 | 20011022 | | |
| US 6037325 | A | 20000314 | US 1998-69823 | 19980430 |
| US 6100238 | A | 20000808 | US 1998-89587 | 19980603 |
| NO 9902734 | A | 19990802 | NO 1999-2734 | 19990604 |

PRIORITY APPLN. INFO.:
US 1994-345820 A2 19941121
US 1996-771317 A2 19961206
US 1996-698575 A1 19960815
US 1996-760916 A 19961206
US 1996-761190 A 19961206
US 1996-761313 A 19961206

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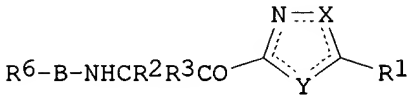
|---|---|---|---|
| US | 1996-762381 | A | 19961206 |
| US | 1997-984881 | A | 19971204 |
| US | 1997-984884 | A | 19971204 |
| US | 1997-985056 | A | 19971204 |
| US | 1997-985201 | A | 19971204 |
| US | 1997-985298 | A | 19971204 |
| WO | 1997-US21636 | W | 19971205 |

OTHER SOURCE(S): MARPAT 132:36032
GI



I

AB Proline analogs I [X, Y = O, S, N or substituted N; R1 = (un)substituted alkyl, alkenyl, or alkynyl, hydroxy, amino, alkylamino, dialkylamino, cycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, cycloalkenyl, alkylcycloalkenyl, alkenylcycloalkenyl, aryl, arylalkyl, arylalkenyl, etc.; R2, R3 = H, (un)substituted alkyl or alkenyl, -RCOR', -RCO2R', -RNR'R''R0, or -RCONR'R'', where R is alkyl or alkenyl and R', R'', and R0 are H, alkyl, alkenyl, cycloalkyl, aryl, cycloalkyl, etc.; B = SO2, CO, OCO, CH2CO; R6 = aryl, arylalkyl, cycloalkyl, alkylcycloalkyl, or R14-A-D-NR7CHR8-, where R7R8 is o-(CH2)nC6H4(CH2)m (m, n = 0, 1), D is a direct bond or an amino acid selected from proline, isoleucine, cyclohexylalanine, or cysteine optionally substituted at sulfur, A is a direct bond, CO, NHCO, SO2, OCO, CH2; R14 = H, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, alkylcycloalkyl, etc.] were prepd. as serine protease inhibitors. Thus, (benzyloxycarbonyl)-L-valyl-N-[1(S)-[[5-(3-methylbenzyl)-1,3,5-oxadiazolyl]carbonyl]-2-methylpropyl]-L-prolinamide was prepd. and showed Ki = 0.025 nM for inhibition of human neutrophil elastase.

IT **208840-22-6P**, CE 2072
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of prolinyl peptide analogs as serine protease inhibitors)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:691089 HCAPLUS
DOCUMENT NUMBER: 131:310839
TITLE: Preparation of heterocyclyl peptide derivatives as cysteine protease inhibitors
INVENTOR(S): Spruce, Lyle W.; Gyorkos, Albert C.; Cheronis, John C.; Goodfellow, Val S.; Leimer, Axel H.; Young, John M.; Gerrity, James I.
PATENT ASSIGNEE(S): Cortech Inc., USA
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9954317 | A1 | 19991028 | WO 1999-US8501 | 19990423 |
| W: | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| US 6004933 | A | 19991221 | US 1998-65258 | 19980423 |
| CA 2329712 | AA | 19991028 | CA 1999-2329712 | 19990423 |
| AU 9939651 | A1 | 19991108 | AU 1999-39651 | 19990423 |
| AU 750369 | B2 | 20020718 | | |

PRIORITY APPLN. INFO.: US 1998-65258 A 19980423
WO 1999-US8501 W 19990423

OTHER SOURCE(S): MARPAT 131:310839

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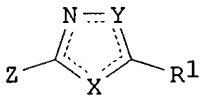


I

AB Compds. I (Z is a cysteine protease binding moiety; R1 = alkyl or alkenyl optionally substituted by halo or hydroxy, alkylamino, dialkylamino, alkyldialkylamino, or cycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, aryl, arylalkyl, or arylalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted by halo, cyano, nitro, amino, alkyl, aryl, etc.; Y, X = O, S, or optionally substituted N) were prepd. as cysteine protease inhibitors. Thus, N-[1(S)-[[5-(3-methylbenzyl)-1,3,4-oxadiazol-2-yl]carbonyl]-2-methylpropyl]-L-phenylalaninamide-(3R)-(isobutyl)succinic acid, prepd. from 3(S)-[(benzyloxycarbonyl)amino]-2-acetoxy-4-methylpentanenitrile, 3-methylphenylacetic hydrazide, 4-methylvaleric acid, (S)-(-)-4-benzyl-2-oxazolidinone, tert-Bu bromoacetate, tert-butyl-(3R)-3-(isobutyl)succinate, and L-phenylalanine Me ester hydrochloride, showed Ki = 85, 3,000, and .apprx.100 nM for inhibition of papain, cathepsin B, and cathepsin L, resp.

IT **208840-22-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclyl peptide derivs. as cysteine protease inhibitors)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:425234 HCAPLUS
DOCUMENT NUMBER: 131:252079
TITLE: Biochemical characterization of .alpha.-ketooxadiazole inhibitors of elastases

AUTHOR(S): Wieczorek, Maciej; Gyorkos, Albert; Spruce, Lyle W.; Ettinger, Anna; Ross, Sherman E.; Kroona, Heather S.; Burgos-Lepley, Carmen E.; Bratton, Larry D.; Drennan, Tyler S.; Garnert, Douglas L.; Von Burg, Gregory; Pilkington, Carolyn G.; Cheronis, John C.
CORPORATE SOURCE: Cortech, Inc., Denver, CO, 80221, USA
SOURCE: Archives of Biochemistry and Biophysics (1999), 367(2), 193-201
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of .alpha.-ketooxadiazole compds. was prepd. and evaluated in vitro as potential inhibitors of human neutrophil elastase (HNE), proteinase-3 (PR-3), and porcine pancreatic elastase (PPE). Several compds. have been found to be very potent, fast, reversible, and selective inhibitors of HNE with Ki values below 100 pM. The highest kon value exceeded 107 M-1 s-1. Some .alpha.-ketooxadiazoles were also very effective against PR-3 and PPE with Ki values in the range of 5-10 nM and 0.1-2 nM, resp. The two rings, 1,2,4- and 1,3,4-oxadiazole, are amenable to substitutions, extending the P' side of the inhibitor and allowing addnl. binding interactions at S' subsites of the enzyme. Nonpeptidic HNE inhibitors contg. the oxadiazole heterocycle displayed promising oral bioavailability. (c) 1999 Academic Press.

IT **208840-22-6P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(biochem. characterization of .alpha.-ketooxadiazole inhibitors of elastases)

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 13 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:231191 HCAPLUS
DOCUMENT NUMBER: 130:252684
TITLE: Preparation of fused cycloheptane azole heterocyclic peptoids as serine protease inhibitors
INVENTOR(S): Gyorkos, Albert; Spruce, Lyle W.
PATENT ASSIGNEE(S): Cortech, Inc., USA
SOURCE: U.S., 61 pp., Cont.-in-part of U.S. 5,618,792.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 18
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5891852 | A | 19990406 | US 1996-762381 | 19961206 |
| US 5618792 | A | 19970408 | US 1994-345820 | 19941121 |
| CA 2205198 | AA | 19960530 | CA 1995-2205198 | 19951117 |
| CN 1170414 | A | 19980114 | CN 1995-196952 | 19951117 |
| ES 2145936 | T3 | 20000716 | ES 1995-940031 | 19951117 |
| ZA 9509819 | A | 19960530 | ZA 1995-9819 | 19951120 |
| TW 474924 | B | 20020201 | TW 1995-84112388 | 19951120 |
| IL 116078 | A1 | 19991231 | IL 1995-116078 | 19951121 |

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|---|---|---|---|---|---|
| US 5874585 | A | 19990223 | US 1996-698575 | 19960815 | |
| US 6015791 | A | 20000118 | US 1997-984881 | 19971204 | |
| WO 9824806 | A2 | 19980611 | WO 1997-US21636 | 19971205 | |
| WO 9824806 | A3 | 19981015 | | | |

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|
| AU 9855894 | A1 | 19980629 | AU 1998-55894 | 19971205 |
| AU 734615 | B2 | 20010621 | | |
| EP 954526 | A2 | 19991110 | EP 1997-952232 | 19971205 |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

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|---|---|---|---|---|
| CN 1247542 | A | 20000315 | CN 1997-180392 | 19971205 |
| BR 9713684 | A | 20000328 | BR 1997-13684 | 19971205 |
| JP 2001507679 | T2 | 20010612 | JP 1998-525656 | 19971205 |
| JP 3220169 | B2 | 20011022 | | |
| JP 2001192398 | A2 | 20010717 | JP 2000-197432 | 19971205 |
| US 6037325 | A | 20000314 | US 1998-69823 | 19980430 |
| NO 9902734 | A | 19990802 | NO 1999-2734 | 19990604 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1994-345820 | A2 | 19941121 |
| US 1996-698575 | A1 | 19960815 |
| US 1996-760916 | A | 19961206 |
| US 1996-761190 | A | 19961206 |
| US 1996-761313 | A | 19961206 |
| US 1996-762381 | A2 | 19961206 |
| US 1996-771317 | A | 19961206 |
| US 1997-984881 | A | 19971204 |
| US 1997-984884 | A | 19971204 |
| US 1997-985056 | A | 19971204 |
| US 1997-985201 | A | 19971204 |
| US 1997-985298 | A | 19971204 |
| JP 1998-525656 | A3 | 19971205 |
| WO 1997-US21636 | W | 19971205 |


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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *


AB The present invention relates to certain substituted oxadiazole, thiadiazole and triazole peptoids I [X, Y = O, N, S; at least one of X or Y = N; R1 = alkyl, alkenyl (un)substituted with halo or OH; alkynyl, alkyl-CO2Me, dialkylamino, alkyldialkylamino; cycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, C5-12 aryl, C5-12 arylalkyl, C5-12 arylalkenyl optionally contg. .gtoreq.1 N, S, O atoms, and optionally substituted; R2, R3, R21, R31 = independently H, alkyl, alkylthio, alkylthioalkyl, cycloalkyl, alkylcycloalkyl, Ph, phenylalkyl optionally substituted with guanidine, carboalkoxy, OH, haloalkyl, alkylthio, alkylguanidine, dialkylguanidine, amidine; B = SO2, CO; R6 = fused cycloheptane ring system Q1-Q3; R13, R15 = independently H, alkyl, halo, alkoxy, carboalkoxy, cycloalkoxy, carboxyl, alkylthio, amino, alkylamino or dialkylamino; aryl, fused aryl, cycloalkyl optionally contg. .gtoreq.1 O,

N, S atoms, and optionally substituted with halo or alkyl; R14 = H, aminoalkyl, alkenyl; (un)substituted cycloalkyl, aryl, arylalkyl, fused aryl-cycloalkyl optionally contg. .gtoreq.1 N, O, S atoms] and pharmaceutically acceptable salts thereof, which are useful as inhibitors of human neutrophil elastase (HNE) for the treatment of HNE-mediated processes implicated in conditions such as adult respiratory distress syndrome, septic shock and multiple organ failure. A series of studies also have indicated the involvement HNE in myocardial ischemia-reperfusion injury, emphysema. R14 = H, aminoalkyl, alkenyl; cycloalkyl, aryl, arylalkyl, fused aryl-cycloalkyl optionally contg. .gtoreq.1 N, O, S atoms, and optionally substituted with alkyl, halo, alkoxy, amino, alkylamino, dialkylamino, carboxy, alkenyl, alkynyl, haloalkoxy, carboalkoxy, alkylcarboxamido, aryl, arylcarboxamido, alkylthio, haloalkylthio;. HNE-mediated processes are implicated in other conditions such as arthritis, periodontal disease, glomerulonephritis, dermatitis, psoriasis, cystic fibrosis, chronic bronchitis, atherosclerosis, Alzheimer's disease, organ transplantation, corneal ulcers, and invasion behavior of malignant tumors. Thus, coupling of hexahydroazepinoindolecarboxylic acid II (Fmoc = 9-fluorenylmethoxycarbonyl) with amino alc. III (prepn. given), followed by Swern oxidn. and deprotection gave desired title compd. IV. IV inhibited human neutrophil elastase with Ki = 10.0 nM.

IT **208840-22-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of fused cycloheptane azole heterocyclic peptoids as serine protease inhibitors)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 14 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:104503 HCAPLUS
DOCUMENT NUMBER: 130:125411
TITLE: Preparation of N-substituted derivatives of azole heterocyclic peptoids as serine protease inhibitors
INVENTOR(S): Gyorkos, Albert; Spruce, Lyle W.
PATENT ASSIGNEE(S): Cortech, Inc., USA
SOURCE: U.S., 63 pp., Cont.-in-part of U.S. Ser. No. 345,820. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 18
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5869455 | A | 19990209 | US 1996-761313 | 19961206 |
| US 5618792 | A | 19970408 | US 1994-345820 | 19941121 |
| CA 2205198 | AA | 19960530 | CA 1995-2205198 | 19951117 |
| CN 1170414 | A | 19980114 | CN 1995-196952 | 19951117 |
| ES 2145936 | T3 | 20000716 | ES 1995-940031 | 19951117 |
| ZA 9509819 | A | 19960530 | ZA 1995-9819 | 19951120 |
| TW 474924 | B | 20020201 | TW 1995-84112388 | 19951120 |
| IL 116078 | A1 | 19991231 | IL 1995-116078 | 19951121 |
| US 5874585 | A | 19990223 | US 1996-698575 | 19960815 |
| US 6001811 | A | 19991214 | US 1997-984884 | 19971204 |
| WO 9824806 | A2 | 19980611 | WO 1997-US21636 | 19971205 |

WO 9824806 A3 19981015
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
AU 9855894 A1 19980629 AU 1998-55894 19971205
AU 734615 B2 20010621
EP 954526 A2 19991110 EP 1997-952232 19971205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
CN 1247542 A 20000315 CN 1997-180392 19971205
BR 9713684 A 20000328 BR 1997-13684 19971205
JP 2001507679 T2 20010612 JP 1998-525656 19971205
JP 3220169 B2 20011022
JP 2001192398 A2 20010717 JP 2000-197432 19971205
US 6037325 A 20000314 US 1998-69823 19980430
NO 9902734 A 19990802 NO 1999-2734 19990604
PRIORITY APPLN. INFO.: US 1994-345820 A2 19941121
US 1996-698575 A1 19960815
US 1996-760916 A 19961206
US 1996-761190 A 19961206
US 1996-761313 A2 19961206
US 1996-762381 A 19961206
US 1996-771317 A 19961206
US 1997-984881 A 19971204
US 1997-984884 A 19971204
US 1997-985056 A 19971204
US 1997-985201 A 19971204
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JP 1998-525656 A3 19971205
WO 1997-US21636 W 19971205
OTHER SOURCE(S): MARPAT 130:125411

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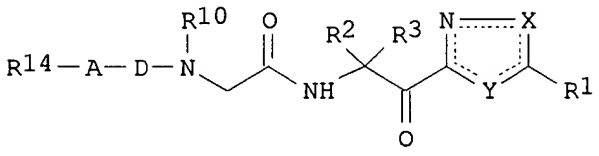

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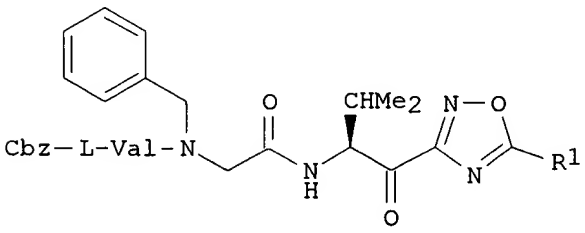

II

AB The present invention relates to certain substituted oxadiazole,

thiadiazole and triazole peptoids I [X, Y = O, N, S; at least one of X or Y = N; R1 = alkyl or alkenyl optionally substituted with halo or hydroxy; alkynyl, alkyl-CO2Me, dialkylamino, alkyldialkylamino; or cycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, C5-12 aryl, C5-12 arylalkyl, C5-12 arylalkenyl optionally contg. 1 or more heteroatoms N, S, O, and optionally substituted; R2, R3 = independently H, alkyl, alkylthio, alkylthioalkyl, cycloalkyl, alkylcycloalkyl, Ph, phenylalkyl optionally substituted with guanidine, carboalkoxy, OH, haloalkyl, alkylthio, alkylguanidine, dialkylguanidine or amidine; R10 = C5-6 aryl, C5-6 arylalkyl, C5-6 arylalkenyl, cycloalkyl, arylcycloalkyl optionally contg. 1 or more heteroatoms N, S, O, and optionally substituted; D = bond, CO, amino acid residue; A = bond, CO, NHCO, SO2, O2C, CH2; R14 = H, alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, fused aryl-cycloalkyl optionally contg. 1 or more heteroatoms N, O, S, and optionally substituted], and pharmaceutically acceptable salts thereof, which are useful as inhibitors of human neutrophil elastase (HNE) for the treatment of HNE-mediated processes implicated in conditions such as adult respiratory distress syndrome, septic shock and multiple organ failure. A series of studies also have indicated the involvement HNE in myocardial ischemia-reperfusion injury, emphysema. HNE-mediated processes are implicated in other conditions such as arthritis, periodontal disease, glomerulonephritis, dermatitis, psoriasis, cystic fibrosis, chronic bronchitis, atherosclerosis, Alzheimer's disease, organ transplantation, corneal ulcers, and invasion behavior of malignant tumors. Thus, oxadiazolyl tripeptoid II (R1 = CH2C6H4CF3-3; Cbz = PhCH2O2C) inhibited human neutrophil elastase with Ki = 0.98 nM.

IT **208840-22-6P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of azole heterocyclic peptoids as serine protease inhibitors)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 15 OF 19 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:56366 HCAPLUS

DOCUMENT NUMBER: 130:125406

TITLE: Preparation of azole heterocyclic peptoids containing keto or diketo ring systems as serine protease inhibitors

INVENTOR(S): Gyorkos, Albert; Spruce, Lyle W.

PATENT ASSIGNEE(S): Cortech, Inc., USA

SOURCE: U.S., 67 pp., Cont.-in-part of U.S. 5,618,792. CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 18

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5861380 | A | 19990119 | US 1996-760916 | 19961206 |
| US 5618792 | A | 19970408 | US 1994-345820 | 19941121 |
| CA 2205198 | AA | 19960530 | CA 1995-2205198 | 19951117 |
| CN 1170414 | A | 19980114 | CN 1995-196952 | 19951117 |
| ES 2145936 | T3 | 20000716 | ES 1995-940031 | 19951117 |
| ZA 9509819 | A | 19960530 | ZA 1995-9819 | 19951120 |
| TW 474924 | B | 20020201 | TW 1995-84112388 | 19951120 |

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| IL 116078 | A1 | 19991231 | IL 1995-116078 | 19951121 | |
| US 5874585 | A | 19990223 | US 1996-698575 | 19960815 | |
| WO 9824806 | A2 | 19980611 | WO 1997-US21636 | 19971205 | |
| WO 9824806 | A3 | 19981015 | | | |

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|---|
| AU 9855894 | A1 | 19980629 | AU 1998-55894 | 19971205 | |
| AU 734615 | B2 | 20010621 | | | |
| EP 954526 | A2 | 19991110 | EP 1997-952232 | 19971205 | |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

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|---|---|---|---|---|---|
| CN 1247542 | A | 20000315 | CN 1997-180392 | 19971205 | |
| BR 9713684 | A | 20000328 | BR 1997-13684 | 19971205 | |
| JP 2001507679 | T2 | 20010612 | JP 1998-525656 | 19971205 | |
| JP 3220169 | B2 | 20011022 | | | |
| JP 2001192398 | A2 | 20010717 | JP 2000-197432 | 19971205 | |
| US 6037325 | A | 20000314 | US 1998-69823 | 19980430 | |
| US 6001814 | A | 19991214 | US 1998-90274 | 19980603 | |
| NO 9902734 | A | 19990802 | NO 1999-2734 | 19990604 | |
| US 2002119985 | A1 | 20020829 | US 2001-927832 | 20010810 | |
| US 2002119998 | A1 | 20020829 | US 2001-991286 | 20011116 | |

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| PRIORITY APPLN. INFO.: | US 1994-345820 | A2 | 19941121 |
| | US 1996-698575 | A1 | 19960815 |
| | US 1996-760916 | A | 19961206 |
| | US 1996-761190 | A | 19961206 |
| | US 1996-761313 | A | 19961206 |
| | US 1996-762381 | A | 19961206 |
| | US 1996-771317 | A | 19961206 |
| | US 1997-984881 | A | 19971204 |
| | US 1997-984884 | A | 19971204 |
| | US 1997-985056 | A | 19971204 |
| | US 1997-985201 | A | 19971204 |
| | US 1997-985298 | A | 19971204 |
| | JP 1998-525656 | A3 | 19971205 |
| | WO 1997-US21636 | W | 19971205 |

OTHER SOURCE(S): MARPAT 130:125406

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to certain substituted oxadiazole, thiadiazole and triazole peptoids I [X, Y = O, N, S; at least one of X or Y = N; R1 = alkyl or alkenyl optionally substituted with halo or hydroxy; alkynyl, alkyl-CO2Me, dialkylamino, alkyldialkylamino; or cycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, C5-12 aryl, C5-12 arylalkyl, C5-12 arylalkenyl optionally contg. 1 or more heteroatoms N, S, O, and optionally substituted; R2, R3 = R'2, R'3 = independently H, alkyl, alkylthio, alkylthioalkyl, cycloalkyl, alkylcycloalkyl, Ph, phenylalkyl optionally substituted with guanidine, carboalkoxy, OH, haloalkyl,

alkylthio, alkylguanidine, dialkylguanidine or amidine; R11, R12 and E together form a monocyclic or bicyclic ring comprising 5-10 atoms selected from C, N, S, and O; said ring contg. 1 or more keto groups; and optionally substituted with halo, cyano, nitro, haloalkyl, amino, aminoalkyl, dialkylamino, alkyl, alkenyl, alkynyl, alkoxy, carboxyl, etc; or cycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, C5-12 aryl, C5-12 arylalkyl, (C5-12 arylalkyl)OCONH, C5-12 arylalkenyl optionally contg. 1 or more heteroatoms N, S, O, and optionally substituted], and pharmaceutically acceptable salts thereof, which are useful as inhibitors of human neutrophil elastase (HNE) for the treatment of HNE-mediated processes implicated in conditions such as adult respiratory distress syndrome, septic shock and multiple organ failure. A series of studies also have indicated the involvement HNE in myocardial ischemia-reperfusion injury, emphysema. HNE-mediated processes are implicated in other conditions such as arthritis, periodontal disease, glomerulonephritis, dermatitis, psoriasis, cystic fibrosis, chronic bronchitis, atherosclerosis, Alzheimer's disease, organ transplantation, corneal ulcers, and invasion behavior of malignant tumors. Thus, coupling of valine-derived oxadiazole II (R1 = CH2C6H4Me-3) (prepn. given) with III (Cbz = PhCH2O2C), followed by oxidn. of the secondary alc. to the corresponding ketone gave oxadiazole peptide deriv. IV. IV inhibited human neutrophil elastase with Ki = 0.21 nM.

IT **208840-22-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of azole heterocyclic peptoids as serine protease inhibitors)

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 16 OF 19 HCAPLUS, COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:721721 HCAPLUS
DOCUMENT NUMBER: 130:4087
TITLE: Preparation of substituted oxadiazole peptide derivatives as cysteine protease inhibitors
INVENTOR(S): Spruce, Lyle W.; Gyorkos, Albert C.; Cheronis, John C.; Goodfellow, Val S.; Leimer, Axel H.; Young, John M.; Gerrity, James Ivan
PATENT ASSIGNEE(S): Cortech, Inc., USA
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9849190 | A2 | 19981105 | WO 1998-US8259 | 19980424 |
| WO 9849190 | A3 | 19990218 | | |

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9871556 A1 19981124 AU 1998-71556 19980424
EP 979242 A2 20000216 EP 1998-918677 19980424
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRIORITY APPLN. INFO.: US 1997-44819P P 19970425
US 1998-65258 A 19980423
WO 1998-US8259 W 19980424
OTHER SOURCE(S): MARPAT 130:4087
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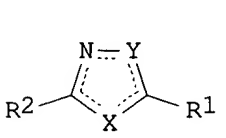
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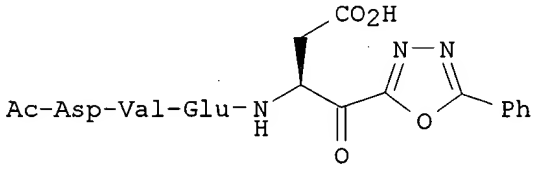
II

AB The present invention relates to cysteine protease inhibitors I [Z = cysteine protease binding moiety, being a carbonyl contg. group, preferably an aminocarbonyl contg. group, wherein the carbon of the heterocycle is attached directly to the carbonyl group of Z; X, Y = independently O, S or N, where N is optionally substituted with alkyl or alkenyl optionally substituted with 1-3 halo atoms; (C5-C6)aryl, arylalkyl or arylalkenyl optionally comprising 1-3 heteroatoms selected from N, O and S, and optionally substituted with halo, cyano, nitro, haloalkyl, amino, aminoalkyl, dialkylamino, alkyl, alkenyl, alkynyl,alkoxy, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamide, arylcarboxamide, alkylthio or haloalkylthio; provided that at least one of Y or X = N; R1 = alkyl or alkenyl (un)substituted with 1-3 halo or hydroxy groups; alkylamino, dialkylamino, alkyldialkylamino; cycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, (C5-12)aryl, (C5-12)arylalkyl, (C5-12)arylalkenyl optionally comprising 1-4 heteroatoms N, O and S, and (un)substituted with halo, cyano, NO2, haloalkyl, amino, aminoalkyl, dialkylamino, alkyl, alkenyl, alkynyl, alkoxy, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamide, (C5-6)aryl, O(C5-6)aryl, arylcarboxamide, alkylthio or haloalkylthio]. Thus, oxadiazolyl peptide II, prepd. in 5 steps from Cbz-Asp(OCMe3)-OH, Ac-Asp(OCMe3)-Val-Gly(OCMe3)-OH, and 2-phenyl-1,3,4-oxadiazole, inhibited caspase 3 with IC50 .ltoreq. 0.1 .mu.M and caspase 6 with IC50 = 6.7 .mu.M. Related oxadiazolyl peptides were prepd. and tested for inhibition of caspase 8, caspase 1, granzyme, papain, cathepsin B, cathepsin L, and gingipain R.

IT **208840-22-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted oxadiazole peptide derivs. as cysteine protease inhibitors)

L2 ANSWER 17 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:604649 HCAPLUS
DOCUMENT NUMBER: 129:231017
TITLE: Preparation of azole heterocyclic peptoids as serine protease inhibitors
INVENTOR(S): Gyorkos, Albert; Spruce, Lyle W.
PATENT ASSIGNEE(S): Cortech, Inc., USA

SOURCE: U.S., 62 pp., Cont.-in-part of U.S. 5,618,792.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 18
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5807829 | A | 19980915 | US 1996-761190 | 19961206 |
| US 5618792 | A | 19970408 | US 1994-345820 | 19941121 |
| CA 2205198 | AA | 19960530 | CA 1995-2205198 | 19951117 |
| CN 1170414 | A | 19980114 | CN 1995-196952 | 19951117 |
| ES 2145936 | T3 | 20000716 | ES 1995-940031 | 19951117 |
| ZA 9509819 | A | 19960530 | ZA 1995-9819 | 19951120 |
| TW 474924 | B | 20020201 | TW 1995-84112388 | 19951120 |
| IL 116078 | A1 | 19991231 | IL 1995-116078 | 19951121 |
| US 5874585 | A | 19990223 | US 1996-698575 | 19960815 |
| US 6159938 | A | 20001212 | US 1997-859242 | 19970520 |
| US 6150334 | A | 20001121 | US 1997-985201 | 19971204 |
| WO 9824806 | A2 | 19980611 | WO 1997-US21636 | 19971205 |
| WO 9824806 | A3 | 19981015 | | |
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| RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9855894 | A1 | 19980629 | AU 1998-55894 | 19971205 |
| AU 734615 | B2 | 20010621 | | |
| EP 954526 | A2 | 19991110 | EP 1997-952232 | 19971205 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| CN 1247542 | A | 20000315 | CN 1997-180392 | 19971205 |
| BR 9713684 | A | 20000328 | BR 1997-13684 | 19971205 |
| JP 2001507679 | T2 | 20010612 | JP 1998-525656 | 19971205 |
| JP 3220169 | B2 | 20011022 | | |
| JP 2001192398 | A2 | 20010717 | JP 2000-197432 | 19971205 |
| US 6037325 | A | 20000314 | US 1998-69823 | 19980430 |
| US 6001813 | A | 19991214 | US 1998-90046 | 19980603 |
| NO 9902734 | A | 19990802 | NO 1999-2734 | 19990604 |

PRIORITY APPLN. INFO.:

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| US 1994-345820 | A2 | 19941121 |
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| US 1996-761190 | A2 | 19961206 |
| US 1996-761313 | A | 19961206 |
| US 1996-762381 | A | 19961206 |
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| US 1997-985056 | A | 19971204 |
| US 1997-985201 | A | 19971204 |
| US 1997-985298 | A | 19971204 |
| JP 1998-525656 | A3 | 19971205 |
| WO 1997-US21636 | W | 19971205 |

OTHER SOURCE(S): MARPAT 129:231017

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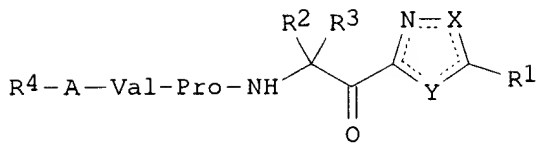

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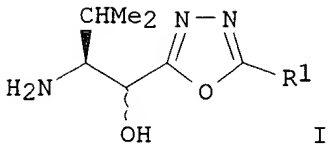

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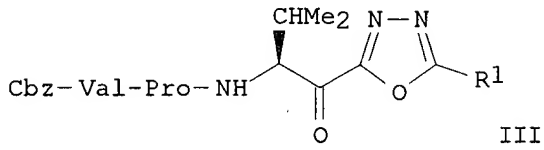


III

AB The present invention relates to certain substituted oxadiazole, thiadiazole and triazole peptoids I [X, Y = O, N, S; at least one of X or Y = N; R1 = alkyl or alkenyl optionally substituted with halo or hydroxy; alkynyl, alkyl-CO2Me, dialkylamino, alkyldialkylamino; or cycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, C5-12 aryl, C5-12 arylalkyl, C5-12 arylalkenyl optionally contg. 1 or more heteroatoms N, S, O, and optionally substituted; R2, R3 = independently H, alkyl, alkylthio, alkylthioalkyl, cycloalkyl, alkylcycloalkyl, Ph, phenylalkyl optionally substituted with guanidine, carboalkoxy, OH, haloalkyl, alkylthio, alkylguanidine, dialkylguanidine or amidine; A = bond, CO, NHCO, SO2, O2C, CH2, amino acid residue; R4 = H, alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, fused aryl-cycloalkyl optionally contg. 1 or more heteroatoms N, O, S, and optionally substituted], and pharmaceutically acceptable salts thereof, which are useful as inhibitors of human neutrophil elastase (HNE) for the treatment of HNE-mediated processes implicated in conditions such as adult respiratory distress syndrome, septic shock and multiple organ failure. A series of studies also have indicated the involvement HNE in myocardial ischemia-reperfusion injury, emphysema. HNE-mediated processes are implicated in other conditions such as arthritis, periodontal disease, glomerulonephritis, dermatitis, psoriasis, cystic fibrosis, chronic bronchitis, atherosclerosis, Alzheimer's disease, organ transplantation, corneal ulcers, and invasion behavior of malignant tumors. Thus, coupling of valine-derived oxadiazole II (R1 = CH2C6H4Me-3) (prepn. given) with Cbz-Val-Pro-OH (Cbz = PhCH2O2C), followed by oxidn. of the secondary alc. to the corresponding ketone gave oxadiazole peptide deriv. III. III inhibited human neutrophil elastase with Ki = 0.025 nM.

IT **208840-22-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of azole heterocyclic peptoids as serine protease inhibitors)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 18 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:585365 HCAPLUS
DOCUMENT NUMBER: 129:216917
TITLE: preparation of proline analog peptides as serine protease inhibitors
INVENTOR(S): Gyorkos, Albert; Spruce, Lyle W.

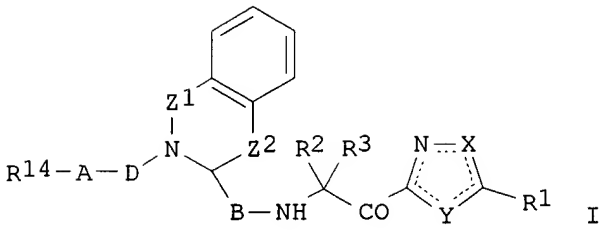
PATENT ASSIGNEE(S): Cortech, Inc., USA
SOURCE: U.S., 62 pp., Cont.-in-part of U. S. 5,618,792.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 18
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5801148 | A | 19980901 | US 1996-771317 | 19961206 |
| US 5618792 | A | 19970408 | US 1994-345820 | 19941121 |
| CA 2205198 | AA | 19960530 | CA 1995-2205198 | 19951117 |
| CN 1170414 | A | 19980114 | CN 1995-196952 | 19951117 |
| ES 2145936 | T3 | 20000716 | ES 1995-940031 | 19951117 |
| ZA 9509819 | A | 19960530 | ZA 1995-9819 | 19951120 |
| TW 474924 | B | 20020201 | TW 1995-84112388 | 19951120 |
| IL 116078 | A1 | 19991231 | IL 1995-116078 | 19951121 |
| US 5874585 | A | 19990223 | US 1996-698575 | 19960815 |
| US 5998379 | A | 19991207 | US 1997-985056 | 19971204 |
| WO 9824806 | A2 | 19980611 | WO 1997-US21636 | 19971205 |
| WO 9824806 | A3 | 19981015 | | |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9855894 | A1 | 19980629 | AU 1998-55894 | 19971205 |
| AU 734615 | B2 | 20010621 | | |
| EP 954526 | A2 | 19991110 | EP 1997-952232 | 19971205 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| CN 1247542 | A | 20000315 | CN 1997-180392 | 19971205 |
| JP 2001507679 | T2 | 20010612 | JP 1998-525656 | 19971205 |
| JP 3220169 | B2 | 20011022 | | |
| JP 2001192398 | A2 | 20010717 | JP 2000-197432 | 19971205 |
| US 6037325 | A | 20000314 | US 1998-69823 | 19980430 |
| US 6100238 | A | 20000808 | US 1998-89587 | 19980603 |
| NO 9902734 | A | 19990802 | NO 1999-2734 | 19990604 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1994-345820 | A2 | 19941121 |
| US 1996-698575 | A1 | 19960815 |
| US 1996-760916 | A | 19961206 |
| US 1996-761190 | A | 19961206 |
| US 1996-761313 | A | 19961206 |
| US 1996-762381 | A | 19961206 |
| US 1996-771317 | A2 | 19961206 |
| US 1997-984881 | A | 19971204 |
| US 1997-984884 | A | 19971204 |
| US 1997-985056 | A | 19971204 |
| US 1997-985201 | A | 19971204 |
| US 1997-985298 | A | 19971204 |
| JP 1998-525656 | A3 | 19971205 |
| WO 1997-US21636 | W | 19971205 |

GI



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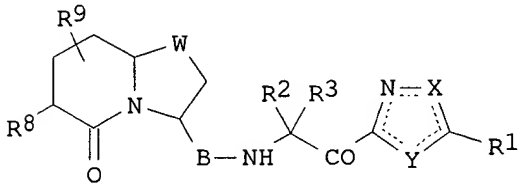

II

AB Proline analog peptides I and II [X, Y = O, N, S; R1 = alkyl, alkenyl, alkynyl, dialkylamino, etc.; R2, R3 = H, alkyl, alkylthio, alkylthioalkyl, etc.; B = SO2, CO; Z1, Z2 = direct bond or CH2; D = direct bond or certain amino acid residues; A = CO, NHCO, SO2, OCO, O2CNH, CH2; R14 = H, alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, etc.; W = S, O; R8 = alkylamino, dialkylamino, amino; R9 = H, alkyl, halo] or their pharmaceutically acceptable salts were prepd. as serine protease inhibitors. Thus, (benzyloxycarbonyl)-L-valyl-N-[1-[2-[5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl]-2-(S)-methylprolyl]-L-prolinamide, prepd. from 3-(S)-[(benzyloxycarbonyl)amino]-2-acetoxy-4-methylpentanenitrile, 3-methylphenylacetic hydrazide, and Cbz-Val-Pro-OH, showed inhibition activity Ki = 0.025 nM.

IT **208840-22-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of proline analog peptides as serine protease inhibitors)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:394350 HCAPLUS
DOCUMENT NUMBER: 129:68032
TITLE: Preparation of oxadiazole peptide analogs as serine protease inhibitors
INVENTOR(S): Gyorkos, Albert; Spruce, Lyle W.
PATENT ASSIGNEE(S): Cortech, Inc., USA; Gyorkos, Albert; Spruce, Lyle W.
SOURCE: PCT Int. Appl., 187 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 18
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9824806 | A2 | 19980611 | WO 1997-US21636 | 19971205 |
| WO 9824806 | A3 | 19981015 | | |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5801148 | A | 19980901 | US 1996-771317 | 19961206 |
| US 5807829 | A | 19980915 | US 1996-761190 | 19961206 |
| US 5861380 | A | 19990119 | US 1996-760916 | 19961206 |
| US 5869455 | A | 19990209 | US 1996-761313 | 19961206 |
| US 5891852 | A | 19990406 | US 1996-762381 | 19961206 |
| US 5998379 | A | 19991207 | US 1997-985056 | 19971204 |
| US 6001811 | A | 19991214 | US 1997-984884 | 19971204 |
| US 6015791 | A | 20000118 | US 1997-984881 | 19971204 |
| US 6150334 | A | 20001121 | US 1997-985201 | 19971204 |
| AU 9855894 | A1 | 19980629 | AU 1998-55894 | 19971205 |
| AU 734615 | B2 | 20010621 | | |
| EP 954526 | A2 | 19991110 | EP 1997-952232 | 19971205 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 9713684 | A | 20000328 | BR 1997-13684 | 19971205 |
| JP 2001507679 | T2 | 20010612 | JP 1998-525656 | 19971205 |
| JP 3220169 | B2 | 20011022 | | |
| NO 9902734 | A | 19990802 | NO 1999-2734 | 19990604 |

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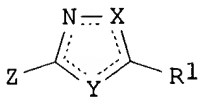
|---|---|---|---|---|
| PRIORITY APPLN. INFO.: | US 1996-760916 | A | 19961206 |
| | US 1996-761190 | A | 19961206 |
| | US 1996-761313 | A | 19961206 |
| | US 1996-762381 | A | 19961206 |
| | US 1996-771317 | A | 19961206 |
| | US 1997-984881 | A | 19971204 |
| | US 1997-984884 | A | 19971204 |
| | US 1997-985056 | A | 19971204 |
| | US 1997-985201 | A | 19971204 |
| | US 1997-985298 | A | 19971204 |
| | US 1994-345820 | A2 | 19941121 |
| | WO 1997-US21636 | W | 19971205 |

OTHER SOURCE(S): MARPAT 129:68032
GI

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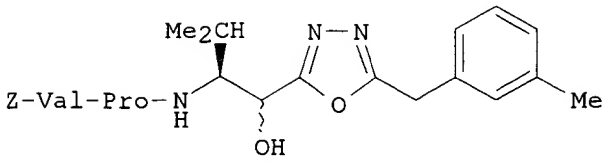
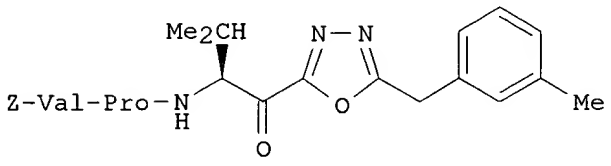



II




III

AB The present invention relates to certain substituted oxadiazole, thiadiazole and triazole peptide analogs I [X, Y = independently O, S, (un)substituted N; Z = serine protease binding moiety, preferably a human neutrophil elastase binding moiety; R1 = (un)substituted alkyl, alkenyl, alkynyl; OH, amino, alkylamino, dialkylamino, cycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, cycloalkenyl, alkylcycloalkenyl, alkenylcycloalkenyl, C5-12 aryl, C5-12 arylalkyl, C5-12 arylalkenyl, fused C5-12 arylcycloalkyl, alkyl fused C5-12 arylcycloalkyl] which are useful as inhibitors of serine proteases. Thus, Swern oxidn. of reduced pseudopeptide II (Z = PhCH2O2C), prepd. in 8 steps from 3S-(benzyloxycarbonylamino)-2-acetoxy-4-methylpentanenitrile, 3-methylphenylacetic hydrazide, and Z-Val-Pro-OH, gave 74% desired oxadiazole III. III inhibited human neutrophil elastase with IC50 = 0.025 nM in an in vitro assay.

IT **208840-22-6P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of oxadiazole peptide analogs as serine protease and human neutrophil elastase inhibitors)

=> d l3 ibib abs hitrn 1-2

L3 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:628010 HCAPLUS
DOCUMENT NUMBER: 133:217681
TITLE: Inhibitors of serine protease activity, and methods and compositions for treatment of **herpes** virus infections
INVENTOR(S): Shapiro, Leland
PATENT ASSIGNEE(S): The Trustees of University Technology Corporation, USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000051625 | A1 | 20000908 | WO 2000-US5557 | 20000303 |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-123167P P 19990305
US 1999-153942P P 19990915
OTHER SOURCE(S): MARPAT 133:217681
AB Compns. and methods of treating and preventing a viral infection are provided. A method of blocking a viral infection facilitated by a serine proteolytic (SP) activity is disclosed, which involves administering to a subject suffering or about to suffer from a viral infection a therapeutically effective amt. of a substance having serine protease inhibitory activity or serpin activity. Among the substances found to be useful are .alpha.1-antitrypsin (AAT), peptide derivs. from the carboxy terminal end of AAT and synthetic drugs mimicking the action of such substances. The invention is particularly well suited for checking a viral infection mediated by members of **herpesviridae** family.
IT **208840-22-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors and methods and compns. for treatment of **herpes** virus infections)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:628008 HCAPLUS
DOCUMENT NUMBER: 133:217724
TITLE: Inhibitors of serine protease activity, and methods and compositions for treatment of nitric oxide-induced clinical conditions

INVENTOR(S): Shapiro, Leland
PATENT ASSIGNEE(S): The Trustees of University Technology Corp., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000051623 | A2 | 20000908 | WO 2000-US5556 | 20000303 |
| WO 2000051623 | A3 | 20001214 | | |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| US 6489308 | B1 | 20021203 | US 2000-518097 | 20000303 |

PRIORITY APPLN. INFO.: US 1999-123167P P 19990305
US 1999-156523P P 19990929

AB A method of treating and preventing diseases is provided. In particular, compns. and methods of blocking diseases assocd. with aberrant levels of nitric oxide and facilitated by a serine proteolytic activity are disclosed, which consist of administering to a subject a therapeutically effective amt. of a compd. having a serine protease inhibitory activity. Among effective compds. are .alpha.1-antitrypsin and synthetic drugs mimicking some or all of the actions of .alpha.1-antitrypsin.

IT **208840-22-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors for treatment of NO-induced diseases)

=> d l5 ibib abs 1-1

L5 ANSWER 1 OF 1 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001119156 EMBASE
TITLE: Molecular targets for antiviral agents.
AUTHOR: De Clercq E.
CORPORATE SOURCE: E. De Clerq, Rega Institute for Medical Research, K. U. Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium. erik.declercq@rega.kuleuven.ac.be
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (2001) 297/1 (1-10).
Refs: 39
ISSN: 0022-3565 CODEN: JPETAB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB There are a number of virus-specific processes within the virus replicative cycle or virus-infected cell that have proven to be attractive targets for chemotherapeutic intervention, i.e., virus adsorption and entry into the cells, reverse (RNA .fwdarw. DNA) transcription, viral DNA polymerization, and cellular enzymatic reactions that are associated with viral DNA and RNA synthesis and viral mRNA maturation (i.e., methylation). A variety of chemotherapeutic agents, both nucleoside (and nucleotide) and non-nucleoside entities, have been identified that specifically interact with these viral targets, that selectively inhibit virus replication, and that are either used or considered for clinical use in the treatment of virus infections in humans. Their indications encompass virtually all major human viral pathogens, including human immunodeficiency virus (HIV), hepatitis B virus (HBV), **herpes** simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), human papilloma virus (HPV), orthomyxoviruses (influenza A and B), paramyxoviruses [e.g., respiratory syncytial virus (RSV)] and hemorrhagic fever viruses (such as Ebola virus).

=> d l17 ibib abs 1-23

L17 ANSWER 1 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-091194 [10] WPIDS
DOC. NO. CPI: C2001-026809
TITLE: Benzothiazinone and benzoxazinone protein kinase inhibitors, used e.g. to affect angiogenesis and treat hyperproliferitive disorders, cancers, arthritis, atherosclerosis, psoriasis, hemangioma, edema, stroke and diabetes.
DERWENT CLASS: B02
INVENTOR(S): ARNOLD, L D; CALDERWOOD, D; DE VEGA, M J P; FERNANDEZ, I F; MATINEZ, J L O; PASCUAL, B G; RAFFERTY, P; GONZALES, P B; ORTEGO, M J L; PEREZ DE VEGA, M J; GONZALEZ PASCUAL, B; ORTEGO MARTINEZ, J L; GONZALES, B P; ORTEGO, J L M; ORTEGO MATINEZ, J L
PATENT ASSIGNEE(S): (BADI) BASF AG; (KNOL) KNOLL GMBH
COUNTRY COUNT: 43
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2000075139 | A2 | 20001214 | (200110)* | EN | 183 |
| RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: AU BG BR CA CN CZ HR HU ID IL IN JP KR MX NO NZ PL RU SG SK TR UA US ZA | | | | | |
| AU 2000051790 | A | 20001228 | (200119) | | |
| EP 1181282 | A2 | 20020227 | (200222) | EN | |
| R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE | | | | | |
| NO 2001005899 | A | 20020130 | (200223) | | |
| BR 2000011063 | A | 20020416 | (200234) | | |
| CZ 2001004244 | A3 | 20020717 | (200260) | | |
| JP 2003501429 | W | 20030114 | (200306) | | 212 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2000075139 | A2 | WO 2000-US15324 | 20000602 |
| AU 2000051790 | A | AU 2000-51790 | 20000602 |
| EP 1181282 | A2 | EP 2000-936476 | 20000602 |
| | | WO 2000-US15324 | 20000602 |
| NO 2001005899 | A | WO 2000-US15324 | 20000602 |
| | | NO 2001-5899 | 20011203 |
| BR 2000011063 | A | BR 2000-11063 | 20000602 |
| | | WO 2000-US15324 | 20000602 |
| CZ 2001004244 | A3 | WO 2000-US15324 | 20000602 |
| | | CZ 2001-4244 | 20000602 |
| JP 2003501429 | W | WO 2000-US15324 | 20000602 |
| | | JP 2001-502421 | 20000602 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---|---|---|

AU 2000051790 A Based on WO 200075139
EP 1181282 A2 Based on WO 200075139
BR 2000011063 A Based on WO 200075139
CZ 2001004244 A3 Based on WO 200075139
JP 2003501429 W Based on WO 200075139

PRIORITY APPLN. INFO: US 1999-137410P 19990603
AN 2001-091194 [10] WPIDS
AB WO 200075139 A UPAB: 20010220
NOVELTY - Benzothiazinone and benzooxazoinone compounds (I) and their physiologically acceptable salts are new.

DETAILED DESCRIPTION - A method of inhibiting one or more protein kinase activities comprising administration of a compound of formula (I) is new:

ring A = optionally substituted;
Q = -N= or -CR2=;
X = S, O or NOR3;
Y = O, S, SO or SO2;
R, R1 = H or an unsubstituted alphatic, aromatic or aralkyl group;
R2 = H, or a substituent;
R3 = H or C(O)R4;
R4 = optionally substituted aliphatic, aromatic or aralkyl group;

and
n = 0-1.

INDEPENDENT CLAIMS are included for:

(1) treatment of a hyperproliferative disorder comprising administration of a compound of formula (I);

(2) a method of affecting angiogenesis comprising administration of a compound of formula (I);

(3) a method of inhibiting vascular hyperpermeability or the production of edema comprising administration of a compound of formula (I);

(4) compounds of formula (Ia) and their salts:
R4 = an optionally substituted aliphatic or aromatic group;
When X = S or NOR3, R = an optionally substituted aromatic or aralkyl group and R1 = H or an optionally substituted aliphatic group;
when X = O and n = 0, R1 = H or an optionally substituted aliphatic group and R is an optionally substituted aromatic or aralkyl group, provided that R is not thiophenyl, **benzoxadiazolyl**, 3-furanyl, 3-pyridinyl or a group of formula (a), where R14 is H, CF3, phenyl, OCH3, O-phenyl, NO2, or OC(O)CH3; and
when X is O and n is 1 R1 is H or an optionally substituted aliphatic group and R is an optionally substituted aromatic or aralkyl group provided that R is not of formula (b) where R15 is H, Cl, CH3, or CF3

ACTIVITY - Cytostatic; antiarthritic; antiarteriosclerotic; antipsoriatic; ophthalmological; antidiabetic; vulnerary; antiulcer; antibacterial; gynecological; antithyroid; cerebroprotective; antiallergic; antiinflammatory; hepatotropic; analgesic; antibacterial; immunosuppressive; virucide; fungicide; anti-HIV; protozoacide; dermatological; antisickling; osteopathic; keratolytic; vasotropic; cardiant; antiviral; antiparasitic; antiprotozoal; antipyretic; circulatory active; antiasthmatic; respiritory active; antiinfertility.

MECHANISM OF ACTION - (I) are protein kinase inhibitors e.g. KDR/FLK-1/VEGFR-2 tyrosine kinase inhibitors and Flt-1/VEGFR-1 tyrosine kinase inhibitors and inhibitors of serine/threonine kinases e.g. CDKs, Plk-1 or Raf-1 and Src kinases e.g. Lck, Src, fyn, and yes.

USE - (I) are used to inhibit protein kinase and to treat hyperproliferative disorders, to affect angiogenesis, to treat cancer,

arthritis, atherosclerosis, psoriasis, hemangioma, myocardial angiogenesis, coronary and cerebral collateral vascularization, ischemic limb angiogenesis, corneal disease, rubeosis, neovascular glaucoma, macular degeneration, retinopathy of prematurity, wound healing, ulcers, Helicobacter-related diseases, fractures, endometriosis, diabetic retinopathy, cat scratch fever, thyroid hyperplasia, burns, trauma, acute lung injury, chronic lung disease, asthma, stroke, polyps, cysts, synovitis, chronic and allergic inflammation, ovarian hyperstimulation syndrome, pulmonary and cerebral edema, keloid, fibrosis, cirrhosis, carpal tunnel syndrome, sepsis, adult respiratory distress syndrome, multiple-organ dysfunction syndrome, ascites and tumor-associated effusions and edema, and to inhibit vascular hyperpermeability or the production of edema (claimed). They may be used to treat ulcers (bacterial, fungal and Mooren ulcers and ulcerative colitis), undesired angiogenesis, edema or stromal deposition occurring in viral infections such as **herpes** simplex, **herpes** zoster, AIDS, psoriasis, Kaposi's sarcoma, protozoan infections, toxoplasmosis, endometriosis, ovarian hyperstimulation syndrome, pre-eclampsia, menometrorrhagia, systemic lupus, sarcoidosis, synovitis, Crohn's disease, sickle cell anemia, Lyme's disease, pemphigoid, Paget's disease, hyperviscosity syndrome, ovarian stimulation syndrome, Osler-Weber-Rendu disease, arthritis, osteoarthritis, edema following trauma, radiation or stroke, ocular and macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser complications, conjunctivitis, anaphylaxis, Stargardt's disease, Eales disease, retinopathy, macular degeneration, cardiovascular conditions (atherosclerosis, restenosis, vascular occlusion, carotid obstructive disease, chronic occlusive pulmonary disease), cancer-related indications (solid tumors, sarcomas especially Ewing's sarcoma and osteosarcoma, retinoblastoma, rhabdomyosarcomas, neuroblastoma, hematopoeitic malignancies including leukemia and lymphoma, tumor-induced pleural or pericardial effusions and malignant ascites), Crow-Fukase (POEMS) syndrome, and diabetic conditions such as glaucoma, diabetic retinopathy and microangiopathy. They also may be used to treat osteopetrosis, tumor-induced hypercalcemia and bone metastases.

ADVANTAGE - Due to the selectivity of (I) for specific kinases, there is a minimization of the side-effects that can occur when less selective kinase inhibitors are employed.

Dwg.0/0

L17 ANSWER 2 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-052651 [04] WPIDS
DOC. NO. CPI: C2000-013524
TITLE: New 3-(3-cyclopentyloxy-4-methoxyphenyl)-3-phenylcyanocyclobutan-1-one derivatives useful as phosphodiesaterase isoenzyme denominated 4 inhibitors.
DERWENT CLASS: B05
INVENTOR(S): CHRISTENSEN, S B; FORSTER, C J
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 22
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9952848 | A1 | 19991021 | (200004)* | EN | 34 |
| RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: CA JP US | | | | | |
| US 6118017 | A | 20000912 | (200046) | | |

US 6172118 B1 20010109 (200104)
EP 1071646 A1 20010131 (200108) EN
R: BE CH DE ES FR GB IT LI NL
JP 2002511439 W 20020416 (200242) 54

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| WO 9952848 | A1 | | WO 1999-US8001 | 19990413 |
| US 6118017 | A | Provisional | US 1998-81643P | 19980414 |
| | | | US 1999-291576 | 19990408 |
| US 6172118 | B1 | Provisional | US 1998-81643P | 19980414 |
| | | | US 1999-291592 | 19990408 |
| EP 1071646 | A1 | | EP 1999-921382 | 19990413 |
| | | | WO 1999-US8001 | 19990413 |
| JP 2002511439 | W | | WO 1999-US8001 | 19990413 |
| | | | JP 2000-543411 | 19990413 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| EP 1071646 | A1 | Based on | WO 9952848 |
| JP 2002511439 | W | Based on | WO 9952848 |

PRIORITY APPLN. INFO: US 1998-81643P 19980414; US 1999-291576 19990408; US 1999-291592 19990408

AN 2000-052651 [04] WPIDS

AB WO 9952848 A UPAB: 20000124

NOVELTY - 3-(3-cyclopentyloxy-4-methoxyphenyl)-3-phenylcyanocyclobutan-1-one derivatives, useful as phosphodiesaterase isoenzyme denominated 4 inhibitors, are new.

DETAILED DESCRIPTION - 3-(3-cyclopentyloxy-4-methoxyphenyl)-3-phenylcyanocyclobutan-1-one derivatives of formula (I) and their salts are new:

R1 = -(CR4R5)nC(O)O(CR4R5)mR6, -(CR4R5)nC(O)NR4(CR4R5)mR6, -(CR4R5)nCO(CR4R5)mR6 or -(CR4R5)rR6, where the alkyl may be substituted with one or more F;

m = 0-2;

n = 1-4;

r = 0-6;

R4, R5 = H or 1-2C alkyl;

R6 = H, methyl, OH, aryl, haloaryl, (halo)aryloxy-(1-3C)-alkyl, indanyl, indenyl, 7-11C polycycloalkyl, (tetrahydro)furanyl, (tetrahydro)pyranyl, (tetrahydro)thienyl, (tetrahydro)thiopyranyl, 3-6C cycloalkyl or 4-6C cycloalkyl with 1-2 unsaturated bonds where cycloalkyl or heterocyclic are optionally substituted with 1-3 methyl, ethyl or OH;

X = VR2, halo, nitro, NR4R5 or formyl amine;

V = O or S(O)m';

q, m' = 0-2;

X2 = O or NR8;

R2 = 1-2C alkyl optionally substituted with 1 or more F;

R3 = H, halo, or 1-4C alkyl optionally substituted by halo, CH2NHC(O)C(O)NH2, CH=CR8'R8', cyclopropyl optionally substituted by R8', CN, OR8, CH2OR8, NR8R10, CH2R8R10, C(=Z)H, C(=O)OR8, C(=O)NR8R10 or CCR8;

Z = O, NR9, NOR8, NCN, C(-CN)2, CR8CN, CR8NO2, C(-CN)C(=O)OR9 and C(-CN)C(=O)NR8R8;

A = O, NR7, NCR4R52-6C alkenyl, NOR14, NOR15, NOCR4R52-6 C alkenyl, NNR4R14, NNR4R15, NCN, NNR8C(O)NR8R14, NNR8R14, NNR8C(=S)NR8R14, 2(1,3-dithiane), 2(1,3-dioxiolane), 2(1,3-dioxane), 2(1,3-dioxathiolane), di(m)ethyl ketal or di(m)ethylthioketal;

R7 = -(CR4R5)qR12 or 1-6C alkyl where R12 or 1-6 alkyl are optionally substituted by 1-3 F, Br, Cl, nitro, NR10R11, C(O)R8, CO2R8, O(CH2)qR8, CN, C(O)NR10R11, O(CH2)qC(O)NR10R11, O(CH2)qC(O)R8, NR10C(O)NR10R11, NR10C(O)R11, NR10C(O)OR9, NR10C(O)OR13, C(NR10)NR10R11, C(NCN)NR10R11, C(NCN)SR9, NR10C(NCN)SR9, NR10C(NCN)NR10R11, NR10S(O)2R9, S(O)mR9, NR10C(O)C(O)NR10R11, NR10C(O)C(O)R10 or R13;

R12 = R13, 3-7C cycloalkyl, (2-, 3-, or 4-pyridyl), pyrimidyl, pyrazolyl, (1-or 2-imidazolyl), pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2-, or 3-thienyl), quinolyl, naphthyl or phenyl;

R8 = H or R9;

R8' = F or R8;

R9 = 1-4C alkyl optionally substituted with 1-3F;

R10 = OR8 or R11;

R11 = H or R9; or

NR10R11 = 5-7 membered ring with at least 1 heteroatom from O, N or S;

R13 = oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl or thiadiazolyl connected through a carbon atom optionally substituted with one or two 1-2C alkyl; and

R14 = H or R7; when R8 and R14 = NR8R14 they form a 5-7 membered ring with at least 1 heteroatom from O, N or sulfur (S) provided that:

R15 = C(O)R14, C(O)R4R14, S(O)2R7 or S(O)2NR4R14:

provided that when R6 = OH, m = 2 and r = 2-6, and when R6 = 2-tetrahydro -pyranyl, -thiopyranyl, -furanyl, or -thienyl, m = 1-2 and r = 1-6, and when n = 1 and m = 0, then R6 is not H in -(CR4R5)nCO(CR4R5)mR6.

INDEPENDENT CLAIMS are also included for the following:

(1) a compound of formula (II) and its salts;

(2) compositions comprising (I) and an excipient; and

(3) compositions comprising (II) and an excipient:

B' = OR14, OR15, SR14, S(O)mR7, S(O)2NR10R14, NR10R14, NR14C(O)R9, NR10C(=Y')R14, NR10C(O)OR7, NR10C(=Y')NR10R14, NR10S(O)2NR10R14, NR10C(NCN)NR10R14, NR10S(O)2R7, NR10C(CR4NO2)NR10R14, NR10C(=N-CN)SR9, NR10C(CR4NO2)SR9, NR10C(NR10)NR10R14, NR10C(O)C(O)NR10R14, C(=Y')R14, C(O)OR14, C(=Y')R14, COOR14, C(=Y')NR10R14, C(NR10)NR10R14, CN, C(=N-OR8)R14, C(=NOR14)R8, C(NR8)NR10R14, C(NR14)NR8R8', C(=N-CN)NR10R14, C(=N-CN)SR11, (2-,4-, or 5-imidazolyl), (3-,4- or 5-pyrazolyl), (4- or 5-triazolyl(1,2,3)), (3- or 5-triazolyl(1,2,4)), 5-tetrazolyl, (2-,4-, or 5-oxazolyl), (3- or 5- oxadiazolyl(1,2,4)), (2-oxadiazolyl(1,3,4)), (2-thiadiazolyl(1,3,4)), (2-,4- or 5-thiazolyl), (2-,4-, or 5-oxazolidinyl), (2-,4-, or 5-thiadiazolinyl) or (2-,4-, or 5-imidazolidinyl) where all heterocyclic rings are optionally substituted with 1 or more R14; and

Y' = O or S:

provided that when R12 is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl or N-morphinolinyl, then q is not 1.

ACTIVITY - Antiasthmatic; airway smooth muscle relaxant; mast cell mediator release inhibitor; neutrophil degranulation suppressant; basophil degranulation inhibitor; monocyte activation inhibitor; macrophage activation inhibitor; fungicide; antiyeast; antiyeast toxicity reducer; fungicide toxicity reducer; virucide.

MECHANISM OF ACTION - Phosphodiesaterase isoenzyme denominated 4 (PDE 4) inhibitor. Tumor Necrosis Factor (TNF) inhibitor.

USE - Used for treating asthma or chronic obstructive pulmonary disease in humans (claimed). Also useful for treating:

(1) allergic and inflammatory diseases e.g. dermatitis, psoriasis, septic shock, Crohn's disease, rheumatoid arthritis and reperfusion injury;

(2) viral infections giving elevated TNF release e.g. human immune deficiency virus (HIV), influenza, adenoviruses, herpes, retroviruses and veterinary viruses; and

(3) yeast or fungal infections giving elevated TNF release e.g. fungal menigitis.

The compounds are also useful for reducing the toxicity of antifungals, antibacterials and antivirals e.g amphotericin B.

ADVANTAGE - The pharmacological action is potentiated by the presence of autocoids and hormones that are released during extrinsic asthmatic attacks.

Dwg.0/0

L17 ANSWER 3 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1997-362977 [33] WPIDS
CROSS REFERENCE: 1995-036375 [05]; 1998-167941 [15]; 2000-205222 [18]; 2002-711569 [77]
DOC. NO. CPI: C1997-116310
TITLE: Treatment of bacterial and parasitic infections - comprises administration of lavendamycin analogue.
DERWENT CLASS: B02
INVENTOR(S): BEHFOROUZ, M; MERRIMAN, R L
PATENT ASSIGNEE(S): (UYBA-N) UNIV BALL STATE
COUNTRY COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| US 5646150 | A | 19970708 | (199733)* | | 31 |

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| US 5646150 | A | CIP of | US 1993-71648 | 19930604 |
| | | | US 1994-345509 | 19941128 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| US 5646150 | A | CIP of | US 5525611 |

PRIORITY APPLN. INFO: US 1994-345509 19941128; US 1993-71648 19930604
AN 1997-362977 [33] WPIDS
CR 1995-036375 [05]; 1998-167941 [15]; 2000-205222 [18]; 2002-711569 [77]
AB US 5646150 A UPAB: 20021204
Treatment of a bacterial or parasitic infection comprises administration of a lavendamycin analogue of formula (I). X = NHC(=O)R10 or NHC(=S)R10; Y = H; OR11, SR11, N(R11)2, NR11N(R11)2, halo, NO2, CN, C(=NR11)R11, C(=O)R12, C(=S)R12 or C(=S)R13; 1-20C alkyl, aryl, 3-8C cycloalkyl, 2-20C alkynyl, 2-20C alkenyl, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isothiazolyl,

isoxazolyl, thiazolyl, **oxadiazolyl** or thiadiazolyl (all optionally substituted by one Rx, NH2, RxNH, (Rx)2N, CN, N3, NO2, OH, halo, SH, RxS, RxSO2, RxSO, RxO, COOH, COORx, CORx, CHO or CON(Rx)2); R4, R6 = H halo, NO2, CN, OR13, SR13, N(R13)2, C(=O)N(R13)2, C(=S)N(R13)2, C(=O)R13, C(=S)R13 or C(=NR13)R13; 1-20C alkyl optionally containing a heteroatom selected from O, S or N, aryl, 3-8C cycloalkyl, 2-20C alkenyl, 2-20C alkynyl, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isothiazolyl, isoxazolyl, thiazolyl, **oxadiazolyl** or thiadiazolyl (all optionally substituted by one Rx, NH2, RxNH, (Rx)2N, CN, N3, NO2, OH, halo, SH, RxS, RxSO2, RxSO, RxO, COOH, COORx, CORx, CHO or CON(Rx)2); R10, R11, R13 = H; 1-20C alkyl, 3-8C cycloalkyl, 2-20C alkenyl, 2-20C alkynyl, aryl, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isothiazolyl, isoxazolyl, thiazolyl, **oxadiazolyl** or thiadiazolyl (all optionally substituted by one Rx, NH2, RxNH, (Rx)2N, CN, N3, NO2, OH, halo, SH, RxS, RxSO2, RxSO, RxO, COOH, COORx, CORx, CHO or CON(Rx)2); R12 = H, N(R11)2, OR11, SR11, NR11N(R11)2, OR14N(R11)2 or 1-20C alkyl, 3-8C cycloalkyl, aryl, 2-20C alkenyl, 2-20C alkynyl, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isothiazolyl, isoxazolyl, thiazolyl, **oxadiazolyl** or thiadiazolyl (all optionally substituted by one Rx, NH2, RxNH, (Rx)2N, CN, N3, NO2, OH, halogen, SH, RxS, RxSO2, RxSO, RxO, COOH, COORx, CORx, CHO or CON(Rx)2); R14 = 1-20C alkylene; Rx = 1-20C alkyl, 3-8C cycloalkyl, aryl, 2-20C alkenyl, 2-20C alkynyl, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isothiazolyl, isoxazolyl, thiazolyl, **oxadiazolyl** or thiadiazolyl.

USE - (I) inhibit the growth of bacteria and parasites and are particularly useful against parasitic infections caused by Leishmania spp. (I) also have antitumour and antiviral effects. (I) are useful for treating both gram positive and gram negative bacteria e.g. bacteria of the genus Staphylococcus, Streptococcus. Viral infections which can be treated using (I) include Retroviridae such as HIV-1, and HIV-2, Herpisviridae such as **herpes** simplex and Epstein-Barr virus, Hepnadnaviridae such as hepatitis B and Picornaviridae. Parasitic infections also include those of Amoeba, Giardia, Babesia, Balantidium, Eimeriorina, Entamoeba, Histomonas, and Trypanosmatidae. (I) are especially effective against solid tumours and malignant tumours.

Dwg.2/2

L17 ANSWER 4 OF 23 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 1997-131824 [12] WPIDS
CROSS REFERENCE: 1993-336568 [42]
DOC. NO. CPI: C1997-042531
TITLE: New 1-phenyl-1-vinyl-cyclohexane derivs. - used as phosphodiesterase IV and TNF prodn. inhibitors, e.g. for treating inflammatory and allergic disease or fungal or viral infections.
DERWENT CLASS: B03 B05
INVENTOR(S): CHRISTENSEN, S B
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| US 5602157 | A | 19970211 | (199712)* | | 17 |

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| US 5602157 | A | CIP of | US 1992-862030 | 19920402 |
| | | CIP of | US 1992-968762 | 19921030 |
| | | CIP of | WO 1993-US1991 | 19930305 |
| | | | US 1995-443641 | 19950518 |

PRIORITY APPLN. INFO: US 1995-443641 19950518; US 1992-862030 19920402; US 1992-968762 19921030; WO 1993-US1991 19930305

AN 1997-131824 [12] WPIDS

CR 1993-336568 [42]

AB US 5602157 A UPAB: 19970320

4-Substd. 1-(3,4-disubstd. phenyl)-1-vinylcyclohexane derivs. of formula (I) and their salts are new. X5 is absent if the optional bond is present; R1 = -(CR4R5)nCOO(CR4R5)mR6, -(CR4R5)nCONR4(CR4R5)mR6, -(CR4R5)nO(CR4R5)mR6 or -(CR4R5)rR6 (in which all alkyl moieties are opt. substd. by one or more halogens); m= 0-2; n = 1-4; r = 0-6; R4,R5 = H, Me or Et; R6 = H, Me, OH, opt. halo-substd. aryl, opt. halo-substd. aryloxy(1-3C)alkyl, indanyl, indenyl, 7-11C polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, 3-6C cycloalkyl or 4-6C cycloalkyl contg. 1 or 2 unsatd. bonds (where cycloalkyl and heterocyclic moieties are opt. substd. by 1-3 Me or one Et); X = YR2, halo, NO2, NR4R5 or HCONH; Y = O, S, SO or SO2; X2 = O or NR8; X3 = H or X; X5 = H, R9, OR8, CN, COR8, COOR8, CON(R8)2 or N(R8)2; R2 = 1-2C alkyl (opt . substd. by at least 1 halogen); s = 0-4; Z = C(Y')R14, COOR14, C(Y')NR10R14, C(NR10)NR10R14, CN, C(NOR8)R14, CONR8NR8COR8, CONR8NR10R14, C(NOR14)R8, C(NR8)NR10R14, C(NR14)N(R8)2, C(NCN)NR10R14, C(NCN)SR9, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-pyrazolyl, 4- or 5-triazolyl(1,2,3), 3- or 5-triazolyl(1,2,4), 5-tetrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 3- or 5-**oxadiazolyl**(1,2,4), 2-**oxadiazolyl** (1,3,4), 2-thiadiazolyl(1,3,4), 2-, 4- or 5-thiazolyl, 2-, 4- or 5-oxazolidinyl, 2-, 4- or 5- thiazolidinyl or 2-, 4- or 5-imidazolidinyl (where all heterocycles are opt. substd. by at least 1 gps. R14); Y' = O or S; R7 = -(CR4R5)qR12 or 1-6C alkyl (where R12 or the 1-6C alkyl gp. is opt. substd. by one or more 1-2C alkyl, itself opt. substd. by 1-3 F); or F, Cl, Br, NO2, NR10R11, COR8, COOR8, OR8, CN, CONR10R11, OCONR10R11, OCOR8, NR10CONR10R11, NR10COR11, NR10COOR9, NR10COR13, C(NR10)NR10R11, C(NCN)NR10R11, C(NCN)SR9, NR10C(NCN)SR9, NR10C(NCN)NR10R11, NR10SO2R9, SR9, SOR9, SO2R9, NR10COCONR10R11, NR10COCOR10, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl or tetrazolyl; q = 0-2; R12 = 3-7C cycloalkyl, 2-, 3- or 4-pyridyl, pyrimidyl, pyrazolyl, 1- or 2-imidazolyl, thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, 2- or 3-thienyl, 4- or 5-thiazolyl, quinolinyl, naphthyl or phenyl; R8 = H or as R9; R81 = R8 or F; R9 = 1-4C alkyl (opt. substd. by 1-3 F); R10 = OR8 or R11; R11 = H or 1-4C alkyl (opt. substd. by 1-3 F); or NR10R11 = 5-7 membered ring opt. contg. at least one additional O, N or S heteroatom; R13 = oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, **oxadiazolyl** or thiadiazolyl (all bonded via C and opt. substd. by 1 or 2 1-2C alkyl); R14 = H or as R7; or NR10R14 may form a ring as for NR10R11; provided that (i) if R6 = OH, then m = 2 or r =2-6, (ii) if R6 = 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl or 2-tetrahydrothienyl, then m = 1 or 2 or r = 1-6,

(iii) if n = 1 and m = 0, then R6 is other than H in -(CR4R5)nO(CR4R5)mR6 and (iv) if R12 = pyrazolyl, imidazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl or morpholinyl (all bonded via N), then q is not 1.

USE - (I) are tumour necrosis factor (TNF) prodn. inhibitors and phosphodiesterase IV (PDE IV) inhibitors, and are used for treating or preventing disorders mediated by TNF or PDE IV. As TNF prodn. inhibitors, (I) are useful for treating viral infections (e.g. infections by cytomegalovirus, adenovirus, influenza virus, **herpes** simplex, **herpes** zoster, veterinary viruses and esp. HIV), treating yeast and fungal infections (esp. fungal meningitis and Candida infections), reducing the toxicity of antifungal, antibacterial or antiviral agents (esp. the antifungal agent amphotericin B) and treating rheumatoid arthritis or spondylitis, osteoarthritis, gouty arthritis, sepsis, septic or endotoxic shock, Gram negative sepsis, toxic shock syndrome, ARDS, cerebral malaria, chronic pulmonary respiratory distress syndrome, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft-versus-host reaction, allograft rejection, fever and myalgia due to infection (e.g. influenza), cachexia secondary to infection, malignancy or AIDS, ARC, AIDS, keloid or scar tissue formation, Crohn's disease, ulcerative colitis, pyresis and autoimmune diseases (e.g. multiple sclerosis, autoimmune diabetes or systemic lupus erythematosus). As PDE IV inhibitors (I) are useful for treating allergic and inflammatory diseases such as asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic or vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and ARDS; and for treating diabetes insipidus and CNS disorders (e.g. depression and multi-infarct dementia). A method for treating an allergic or inflammatory disease using (I) is claimed.

Dwg.0/0

L17 ANSWER 5 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-321768 [32] WPIDS
DOC. NO. CPI: C1996-102463
TITLE: New 1,4-disubstd. 4-phenyl-cyclohexene derivs. - used as TNF prodn. and phosphodiesterase inhibitors, e.g. for treating allergy, inflammation or viral or fungal infections.
DERWENT CLASS: B05 C02 C03
INVENTOR(S): BENDER, P E; CHRISTENSEN, S B; KARPINSKI, J M; RYAN, M D; RYAN, M
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 19
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9620175 | A1 | 19960704 | (199632)* | EN | 31 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: JP US | | | | | |
| EP 799205 | A1 | 19971008 | (199745) | EN | |
| R: BE CH DE DK FR GB IT LI NL | | | | | |
| JP 10513153 | W | 19981215 | (199909) | | 43 |
| EP 799205 | B1 | 19990908 | (199941) | EN | |
| R: BE CH DE DK FR GB IT LI NL | | | | | |
| DE 69512086 | E | 19991014 | (199949) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9620175 | A1 | WO 1995-US16694 | 19951221 |
| EP 799205 | A1 | EP 1995-944511 | 19951221 |
| | | WO 1995-US16694 | 19951221 |
| JP 10513153 | W | WO 1995-US16694 | 19951221 |
| | | JP 1996-520522 | 19951221 |
| EP 799205 | B1 | EP 1995-944511 | 19951221 |
| | | WO 1995-US16694 | 19951221 |
| DE 69512086 | E | DE 1995-612086 | 19951221 |
| | | EP 1995-944511 | 19951221 |
| | | WO 1995-US16694 | 19951221 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| EP 799205 | A1 | Based on | WO 9620175 |
| JP 10513153 | W | Based on | WO 9620175 |
| EP 799205 | B1 | Based on | WO 9620175 |
| DE 69512086 | E | Based on | EP 799205 |
| | | Based on | WO 9620175 |

PRIORITY APPLN. INFO: US 1994-363168 19941223
AN 1996-321768 [32] WPIDS
AB WO 9620175 A UPAB: 19960819
4-(3,4-Disubstd. phenyl)- 1,4-disubstd. or 1,2,4-trisubstd. cyclohexene derivs. of formula (I) and their salts are new: Z1 = Z and Z2 = H, i.e. cpds. (I'); or Z1 = Z'' and Z2 = Z', i.e. cpds. (I''); R1 = -(CR4R5)nCOO(CR4R5)mR6, -(CR4R5)nCONR4(CR4R5)mR6, -(CR4R5)nO(CR4R5)mR6 or -(CR4R5)rR6; where the alkyl moieties are opt. substd. by halogen(s); m = 0-2; n = 0-4; r = 0-6; R4, R5 = H, Me or Et; R6 = H, Me, OH, opt. halo substd. aryl, opt. halo substd. aryloxy(1-3C)alkyl, indanyl, indenyl, 7-11C polycycloalkyl, furanyl, pyranyl, thienyl, thiopyranyl (the last four opt. as tetrahydro derivs.), 3-6C cycloalkyl or 4-6C cycloalkyl contg. 1 or 2 unsatd. bonds, where cycloalkyl or heterocyclic moieties are opt. substd. by 1-3 Me, one Et or one OH; provided that (a) if R6 = OH, then m = 2 or r = 2-6, (b) if R6 = 2-tetrahydro(pyranyl, thiopyranyl, thienyl or furanyl), then m = 1 or 2 or r = 1-6 and (c) if m = 1 and n = 0, then R6 is other than H in -(CR4R5)nO(CR4R5)mR6; X = YR2, F, NR4R5 or HCONH; Y = O or S(O)m'; m' = 0-2; X2 = O or NR8; X3 = H or X; R2 = methyl or ethyl, both opt. substd. by halogen(s); s = 0-4; W = 2-6C alkylene, 2-6C alkenylene or 2-6C alkynylene; R3 = substd. carboxy, carbamide or alkyl; Z= CN or opt. substd. thio, alcohol, ester carboxamide, 2-, 4- or 5-imidazolyl, pyrazolyl, 1,2,3-triazol-4- or 5-yl, 1,2,4-triazol-3- or 5-yl, 5-tetrazolyl, oxazolyl, isoxazolyl, 1,2,4- or 1,3,4-**oxadiazolyl**, 1,3,4-thiadiazolyl, thiazolyl, 2-, 4- or 5-oxazolidinyl, 2-, 4- or 5-thiazolidinyl or 2-, 4- or 5-imidazolidinyl; R8 = H or as R11; R11 = 1-4C alkyl (opt. substd. by 1-3 F).

USE - (I) inhibit phosphodiesterase IV (PDE IV) and prodn. of tumour necrosis factor (TNF). They are used for treatment or prophylaxis of PDE IV- or TNF-mediated diseases, specifically: (i) allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of

the myocardium and brain, chronic glomerulonephritis, endotoxin shock and ARDS; (ii) diabetes insipidus and CNS disorders such as depression and multiinfarct dementia; (iii) viral infections, esp. infections by HIV, cytomegalovirus, influenza virus, adenovirus, **herpes** simplex, **herpes** zoster or animal viruses (e.g. FIV, equine infectious anaemia, caprine arthritis, visna or maedi virus), partic. HIV; and (iv) yeast and fungal infections, esp. fungal meningitis. (I) are also useful for reducing the toxicity of antifungal, antibacterial or antiviral agents, specifically amphotericins, partic. amphotericin B.
Dwg.0/0

L17 ANSWER 6 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-321767 [32] WPIDS
DOC. NO. CPI: C1996-102462
TITLE: New 1,3-di substd. 1-phenyl-cyclohexane derivs. - used as TNF prodn. and phosphodiesterase inhibitors, e.g., for treating allergy, inflammation and viral or fungal infections.
DERWENT CLASS: B05 C02 C03
INVENTOR(S): BENDER, P E; CHRISTENSEN, S B; KARPINSKI, J M; RYAN, M D; RYAN, M
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 19
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9620174 | A1 | 19960704 | (199632)* | EN | 24 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: JP US | | | | | |
| EP 799204 | A1 | 19971008 | (199745) | EN | |
| R: BE CH DE DK FR GB IT LI NL | | | | | |
| JP 10511395 | W | 19981104 | (199903) | | 33 |
| US 5900417 | A | 19990504 | (199925) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9620174 | A1 | WO 1995-US16709 | 19951221 |
| EP 799204 | A1 | EP 1995-943941 | 19951221 |
| | | WO 1995-US16709 | 19951221 |
| JP 10511395 | W | WO 1995-US16709 | 19951221 |
| | | JP 1996-520527 | 19951221 |
| US 5900417 | A | WO 1995-US16709 | 19951221 |
| | | US 1996-596244 | 19960227 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| EP 799204 | A1 | Based on | WO 9620174 |
| JP 10511395 | W | Based on | WO 9620174 |
| US 5900417 | A | Based on | WO 9620174 |

PRIORITY APPLN. INFO: US 1994-362727 19941223; US 1996-596244 19960227
AN 1996-321767 [32] WPIDS

AB WO 9620174 A UPAB: 19960819
1,3-Disubstd. or 1,3,3-trisubstd. 1-(3,4-disubstd. phenyl)- cyclohexane derivs. of formula (I) and their salts are new: R1 = -(CR5R5)nCOO(CR4R5)mR6, -(CR4R5)nCONR4(CR4R5)mR6, -(CR4R5)nO(CR4R5)mR6 or -(CR4R5)rR6, where alkyl moieties are opt. substd. by one or more F; m = 0-2; n = 0-4; r = 0-6; R4, R5 = H, Me or Et; R6 = H, Me, OH, opt. halo-substd. aryl, opt. substd. aryloxy-(1-3C)-alkyl, indanyl, indenyl, 7-11C polycycloalkyl, furanyl, pyranyl, thienyl, thiopyranyl (the last four opt. as tetrahydro derivs.), 3-6C cycloalkyl or 4-6C cycloalkyl contg. 1 or 2 unsatd. bonds, where cycloalkyl and heterocyclic moieties are opt. substd. by 1-3 Me, one Et or one OH; provided that (a) if R6 = OH, then m = 2 or r = 2-6, (b) if R6 = 2-tetrahydro(pyranyl, thiopyranyl, furanyl or thienyl), then m = 1 or 2 or r = 1-6 or (c) if n = 1 and m = 0, then R6 is other than H in -(CR4R5)nO(CR4R5)mR6; X = YR2, F, NR4R5 or HCONH; Y = O or S(O)m'; m' = 0-2; X2 = O or NR8; X3 = H or X; R2 = methyl or ethyl, both opt. substd. by one or more F; R3 = COOR14, CONR4R14 or R7; W = 2-6C alkylene, 2-6C alkenylene or 2-6C alkynylene; s = 0-4; Z = -C(R8)2-Z'; R8 = H or R9; R9 = 1-4C alkyl (opt. substd. by 1-3 F); R7 = substd. alkyl; Z' = e.g. CN, tetrazolyl, imidazolyl, imidazolinyl, pyrazolyl, thiazolyl, oxazolyl, oxazolidinyl, triazolyl, isoxazolyl, **oxadiazolyl**, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or opt. substd. hydroxy, thio, sulphinyl, sulphonyl, amino or carboxy.

USE - (I) inhibit phosphodiesterase IV (PDE IV) and prodn. of tumour necrosis factor (TNF). They are used for treatment or prophylaxis of PDE IV- or TNF-mediated diseases, specifically: (i) allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxin shock and ARDS; (ii) diabetes insipidus and CNS disorders such as depression and multiinfarct dementia; (iii) viral infections, esp. infections by HIV, cytomegalovirus, influenza virus, adenovirus, **herpes** simplex, **herpes** zoster or animal viruses (e.g. FIV, equine infectious anaemia, caprine arthritis, visna or maedi virus), partic. HIV; and (iv) yeast and fungal infections, esp. fungal meningitis. (I) are also useful for reducing the toxicity of antifungal, antibacterial or antiviral agents, specifically amphotericins, partic. amphotericin B.
Dwg.0/0

L17 ANSWER 7 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-321758 [32] WPIDS
DOC. NO. CPI: C1996-102453
TITLE: New bis-phenyl cyclohexenyl-aliphatic hydrocarbon derivs. - used as TNF prodn. and phosphodiesterase inhibitors, e.g. for treating allergy, inflammation or viral or fungal infections.
DERWENT CLASS: B05 C02 C03
INVENTOR(S): CHRISTENSEN, S B; KARPINSKI, J M
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 19
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9620162 | A1 | 19960704 | (199632)* | EN | 26 |

RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE

W: JP US
EP 799186 A1 19971008 (199745) EN
R: BE CH DE DK FR GB IT LI NL
US 5777160 A 19980707 (199834)
JP 10511390 W 19981104 (199903) 36

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| WO 9620162 | A1 | | WO 1995-US13322 | 19951010 |
| EP 799186 | A1 | | EP 1995-938261 | 19951010 |
| | | | WO 1995-US13322 | 19951010 |
| US 5777160 | A | Cont of | US 1994-363179 | 19941223 |
| | | | WO 1995-US13322 | 19951010 |
| | | | US 1997-860295 | 19970623 |
| JP 10511390 | W | | WO 1995-US13322 | 19951010 |
| | | | JP 1996-520433 | 19951010 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| EP 799186 | A1 | Based on | WO 9620162 |
| US 5777160 | A | Based on | WO 9620162 |
| JP 10511390 | W | Based on | WO 9620162 |

PRIORITY APPLN. INFO: US 1994-363179 19941223; US 1997-860295 19970623

AN 1996-321758 [32] WPIDS

AB WO 9620162 A UPAB: 19960819

Bis-(1-phenyl-4-substd. or 3,4-disubstd. cyclohex-3-enyl)-alkane, alkene or alkyne derivs. of formula (I) and their salts are new.Z1 = Z and Z2 = H, i.e. cpds. (I'); or Z1 = Z'' and Z2 = Z', i.e. cpds. (I''); R1 = -(CCR4R5)nCOO(CR4R5)mR6, -(CR4R5)nCONR4(CR4R5)mR65, -(CR4R5)nO(CR4R5)mR6 or -(CR4R5)rR6, where alkyl moieties are opt. substd. by halogen(s); R4, R5 = H, Me or Et; m = 0-2; n = 1-4; r = 0-6; R6 = H, Me, OH, opt. halo-substd. aryl, opt. halo substd.aryloxy-(1-3C)alkyl, indanyl, indenyl, 7-11C polycycloalkyl, furanyl pyranyl, thienyl, thiopyranyl (the last four opt. ashtetrahydro derivs.), 3-6C cycloalkyl or 4-6C cycloalkyl contg. 1 or 2 unsatd. bonds, where cycloalkyl and heterocyclic moieties are opt. substd. by 1-3 Me, one Et or one OH; provided that (a) if R6 = OH, then m = 2 or r = 2-6, (b) if R6 = 2-tetrahydro(pyranyl, thiopyranyl, furanyl or thienyl), then m = 1 or 2 or r = 1-6 and (c) if n = 1 and m = 0, then R6 is other than H in -(CR4R5)nO(CR4R5)+mR+6; X = YR2, F, NR4R5 or NCONH; Y = O or S(O)m'; m' = 0-2; X2 = O or NR8; X3 = H or X; R2 = methyl or ethyl, both opt. substd. by halogen(s); s = 0-4; W = 2-6C alkylene, 2-6C alkenylene or 2-6C alkynylene; Z, Z'' =e.g S(O)m'R9, OSO2R9, OR9, O(CR4R5)nOR9 or N(R9)2; Z '= CN or opt. substd. thiol, alcohol, carbamido or 2-, 4- or 5-imidazolyl, pyrazolyl, 1,2,3-triazol-4- or 5-yl, 1,2,4-triazol-3- or 5-yl, 5-tetrazolyl, oxazolyl, isoxazolyl, 1,2,4- or 1,3,4-**oxadiazolyl**, 1,3,4-thiadiazolyl, thiazolyl, 2-, 4- or 5-oxazolidinyl, 2-, 4- or 5-thiazolidinyl or 2-, 4- or 5-imidazolidinyl, R8 = H or R11; R9 = 1-10C alkyl, 2-10C alkenyl, 3-7C cycloalkyl, 4-6C cycloalkenyl, aryl, aralkyl, heteroaryl or heteroaralkyl, all opt. substd. by one or more F; R11 = 1-4C alkyl (opt. substd. by 1-3 F).

USE - (I) inhibit phosphodiesterase IV (PDE IV) and prodn. of tumour necrosis factor (TNF). They are used for treatment or prophylaxis of

PDE-IV- or TNF-mediated diseases, specifically: (i) allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivities, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxin shock and ARDS; (ii) diabetes insipidus and CNS disorders such as depression and multiinfarct dementia; (iii) viral infections, esp. infections by HIV, cytomegalovirus, influenza virus, adenovirus, **herpes** simplex, **herpes** zoster or animal viruses (e.g. FIV, equine infectious anaemia, caprine arthritis, visna or maedi virus), partic. HIV; and (iv) yeast and fungal infections, esp. fungal meningitis. (I) are also useful for reducing the toxicity of antifungal antibacterial or antiviral agents, specifically amphotericins, partic. amphotericin B.
Dwg.0/0

L17 ANSWER 8 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-321755 [32] WPIDS
CROSS REFERENCE: 1996-341947 [34]
DOC. NO. CPI: C1996-102450
TITLE: New 3,3-di substd. cyclohexan-1-ylidine acetate derivs. - for treating allergic and inflammatory diseases, also inhibitors of tumour necrosis factor prodn..
DERWENT CLASS: B03 B05 C02 C03
INVENTOR(S): BENDER, P E; CHRISTENSEN, S B; KARPINSKI, J M; RYAN, M D
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 18
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9620159 | A1 | 19960704 | (199632)* | EN | 25 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: JP US | | | | | |
| JP 2002503200 | W | 20020129 | (200211) | | 35 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9620159 | A1 | WO 1995-US16293 | 19951214 |
| JP 2002503200 | W | WO 1995-US16293 | 19951214 |
| | | JP 1996-520488 | 19951214 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---|---|---|
| JP 2002503200 | W Based on | WO 9620159 |

PRIORITY APPLN. INFO: US 1994-363665 19941223
AN 1996-321755 [32] WPIDS
CR 1996-341947 [34]
AB WO 9620159 A UPAB: 20020215
Phenyl-cyclohexan-1-ylidene acetate derivs. of formula (I) and their salts are new. R1 = (CR4R5)nCOO(CR4R5)mR6, (CR4R5)nCONR4(CR4R5)mR6, (CR4R5)rR6 or (CR4R5)nO(CR4R5)mR6; in which alkyl may be substd. by 1 or more halo; m = 0-2; n = 0-4; r = 0-6; each R4 and R5 = H, Me or Et; R6 = H, Me, OH,

aryl or aryloxy(1-3C)alkyl (both opt. substd. by halo), indanyl, indenyl, 7-11C polycycloalkyl, (tetrahydro)furanyl, (tetrahydro)pyranyl, (tetrahydro)thienyl, (tetrahydro)thiopyranyl, 3-6C cycloalkyl, or 4-6C cycloalkyl with 1 or 2 unsatd. bonds; cycloalkyl and heterocyclic gps. are opt. substd. by 1-3 Me, one ET or OH; provided that (a) when R6 = OH, m = 2 or r = 2-6; (b) when R6 = 2-tetrahydro-pyranyl, -thiopyranyl, -furanyl or -thienyl, m = 1 or 2, or r = 1-6; (c) when n = 1 and m = 0 then R6 is not H in (CR4R5)nO(CR4R5)mR6; X = YR2, F, NR4R5 or formyl amine; Y = O or SOm'; m' = 0-2; X2 = O or NR8; X3 = H or X; X4 = H, R9, OR8, CN, COR8, COOR8, CONR8R8 or NR8R8; R2 = Me or Et, opt. substd. by 1 or more halo; s = 0-4; W = 2-6C alkyl, alkenyl or alkynyl; R3 = e.g opt. substd ester, amide, alkyl, oxazolidinyl, oxazolyl, thiazolyol, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, **oxadiazolyl** or thiadiazoyl; Z= e.g opt substd. ester, amide or cyanomethyl

USE - (I) inhibit phosphodiesterase IV (PDE IV) and prodn. of tumour necrosis factor (TNF). They are used for treatment or prophylaxis of PDE-IV- or TNF-mediated diseases, specifically: (i) allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivities, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxin shock and ARDS; (ii) diabetes insipidus and CNS disorders such as depression and multiinfarct dementia; (iii) viral infections, esp. infections by HIV, cytomegalovirus, influenza virus, adenovirus, **herpes** simplex, **herpes** zoster or animal viruses (e.g. FIV, equine infectious anaemia, caprine arthritis, visna or maedi virus), partic. HIV; and (iv) yeast and fungal infections, esp. fungal meningitis. (I) are also useful for reducing the toxicity of antifungal antibacterial or antiviral agents, specifically amphotericins, partic. amphotericin B.

Dwg.0/0

L17 ANSWER 9 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-321753 [32] WPIDS
DOC. NO. CPI: C1996-102448
TITLE: New bis-phenylcyclohexanol substd. alkane, alkene and alkyne derivs. - for treating allergic and inflammatory diseases, also inhibitors of tumour necrosis factor prodn..
DERWENT CLASS: B03 B05 C02 C03
INVENTOR(S): CHRISTENSEN, S B; KARPINSKI, J M
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 19
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9620157 | A1 | 19960704 | (199632)* | EN | 26 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: JP US | | | | | |
| EP 799182 | A1 | 19971008 | (199745) | EN | |
| R: BE CH DE DK FR GB IT LI NL | | | | | |
| US 5723681 | A | 19980303 | (199816) | | 10 |
| JP 10511391 | W | 19981104 | (199903) | | 37 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9620157 | A1 | WO 1995-US13323 | 19951010 |
| EP 799182 | A1 | EP 1995-936355 | 19951010 |
| | | WO 1995-US13323 | 19951010 |
| US 5723681 | A | WO 1995-US13323 | 19951010 |
| | | US 1997-860288 | 19970623 |
| JP 10511391 | W | WO 1995-US13323 | 19951010 |
| | | JP 1996-520434 | 19951010 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| EP 799182 | A1 | Based on | WO 9620157 |
| US 5723681 | A | Based on | WO 9620157 |
| JP 10511391 | W | Based on | WO 9620157 |

PRIORITY APPLN. INFO: US 1994-362708 19941223; US 1997-860288 19970623

AN 1996-321753 [32] WPIDS

AB WO 9620157 A UPAB: 19960819

Phenylcyclohexanol derivs. of formula (I) and their salts are new. R1 = (CR4R5)nCOO(CR4R5)mR6, (CR4R5)nCONR4(CR4R5)mR6, (CR4R5)nO(CR4R5)mR6 or (CR4R5)rR6 in which alkyl gps. are opt. substd. by 1 or more F; m = 0-2; n = 1-4; r = 0-6; R4, R5 = H or (m)ethyl; R6 = H, Me, OH, aryl or aryloxy(1-3C)alkyl (both opt. substd. by halo), indanyl, indenyl, 7-11C polycycloalkyl, tetrahydro-furanyl, -pyranyl, -thienyl or -thiopyranyl, 3-6C cycloalkyl or 4-6C cycloalkyl with 1 or 2 unsatd. bonds; áll cycloalkyl and heterocyclic gps. are opt. substd. by 1-3 Me or by 1 Et or OH; provided that when R6 = OH, thén m = 2 or r = 2-6; or when R6 = 2-tetrahydro-pyranyl, -thiopyranyl, -furanyl or -thienyl, then m = 1 or 2 or r = 1-6; or when n = 1 and m = 0, then R6 is not H in (CR4R5)nO(CR4R5)mR6; X = YR2, F, NR4R5 or formyl amine;Y = O or SOm; m' = 0-2; W = 2-6C alkyl, alkenyl or alkynyl; each X2 = O or NR8; each X3 = H, or X; R2 = Me or Et, opt. substd. by 1 or more F; s = 0-4; R8 = H or R9; R9 = 1-4C alkyl opt substd. by 1-3 F; Z= e.g. opt. substd. ether, thiol, sulphinyl, sulphonyl, amino, oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinylisoxazolyl, **oxadiazolyl** or thiadiazolyl

USE - (I) inhibit phosphodiesterase IV (PDE IV) and prodn. of tumour necrosis factor (TNF). They are used for treatment or prophylaxis of PDE-IV- or TNF-mediated diseases, specifically: (i) allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivities, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxin shock and ARDS; (ii) diabetes insipidus and CNS disorders such as depression and multiinfarct dementia; (iii) viral infections, esp. infections by HIV, cytomegalovirus, influenza virus, adenovirus, **herpes** simplex, **herpes** zoster or animal viruses (e.g. FIV, equine infectious anaemia, caprine arthritis, visna or maedi virus), partic. HIV; and (iv) yeast and fungal infections, esp. fungal meningitis. (I) are also useful for reducing the toxicity of antifungal antibacterial or antiviral agents, specifically amphotericins, partic. amphotericin B.

Dwg.0/0

ABEQ US 5723681 A UPAB: 19980421

Phenylcyclohexanol derivs. of formula (I) and their salts are new. R1 = (CR4R5)nCOO(CR4R5)mR6, (CR4R5)nCONR4(CR4R5)mR6, (CR4R5)nO(CR4R5)mR6 or (CR4R5)rR6 in which alkyl gps. are opt. substd. by 1 or more F; m = 0-2; n = 1-4; r = 0-6; R4, R5 = H or (m)ethyl; R6 = H, Me, OH, aryl or aryloxy(1-3C)alkyl (both opt. substd. by halo), indanyl, indenyl, 7-11C polycycloalkyl, tetrahydro-furanyl, -pyranyl, -thienyl or -thiopyranyl, 3-6C cycloalkyl or 4-6C cycloalkyl with 1 or 2 unsatd. bonds; all cycloalkyl and heterocyclic gps. are opt. substd. by 1-3 Me or by 1 Et or OH; provided that when R6 = OH, then m = 2 or r = 2-6; or when R6 = 2-tetrahydro-pyranyl, -thiopyranyl, -furanyl or -thienyl, then m = 1 or 2 or r = 1-6; or when n = 1 and m = 0, then R6 is not H in (CR4R5)nO(CR4R5)mR6; X = YR2, F, NR4R5 or formyl amine;Y = O or SOm; m' = 0-2; W = 2-6C alkyl, alkenyl or alkynyl; each X2 = O or NR8; each X3 = H, or X; R2 = Me or Et, opt. substd. by 1 or more F; s = 0-4; R8 = H or R9; R9 = 1-4C alkyl opt substd. by 1-3 F; Z= e.g. opt. substd. ether, thiol, sulphinyl, sulphonyl, amino, oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinylisoxazolyl, **oxadiazolyl** or thiadiazolyl

USE - (I) inhibit phosphodiesterase IV (PDE IV) and prodn. of tumour necrosis factor (TNF). They are used for treatment or prophylaxis of PDE-IV- or TNF-mediated diseases, specifically: (i) allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivities, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxin shock and ARDS; (ii) diabetes insipidus and CNS disorders such as depression and multiinfarct dementia; (iii) viral infections, esp. infections by HIV, cytomegalovirus, influenza virus, adenovirus, **herpes** simplex, **herpes** zoster or animal viruses (e.g. FIV, equine infectious anaemia, caprine arthritis, visna or maedi virus), partic. HIV; and (iv) yeast and fungal infections, esp. fungal meningitis. (I) are also useful for reducing the toxicity of antifungal antibacterial or antiviral agents, specifically amphotericins, partic. amphotericin B.

Dwg.0/0

L17 ANSWER 10 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-321634 [32] WPIDS
DOC. NO. CPI: C1996-102371
TITLE: New substd. phenyl-cyclohexene and cyclohexanone derivs - are useful in treatment of allergic disorders, inflammatory disorders, viral infections, fungal infections, etc.
DERWENT CLASS: B03 B05 C02 C03
INVENTOR(S): BENDER, P E; CHRISTENSEN, S B; KARPINSKI, J M; RYAN, M D; RYAM, M D; RYAN, D M
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 67
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9619995 | A1 | 19960704 | (199632)* | EN | 58 |

RW: AT BE CH DE DK ES FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AM AU BB BG BR BY CA CN CZ EE FI GE HU IS JP KE KG KP KR KZ LK LR LT LV MD MG MN MX NO NZ PL PT RO RU SD SG SI SK TJ TM TT UA US UZ VN

| | | | | |
|---|---|---|---|---|
| ZA 9510884 | A | 19960828 (199639) | 57 | |
| AU 9646883 | A | 19960719 (199647) | | |
| NO 9702898 | A | 19970820 (199744) | | |
| EP 800393 | A1 | 19971015 (199746) | EN | |
| R: BE CH DE DK FR GB IT LI NL | | | | |
| FI 9702673 | A | 19970819 (199747) | | |
| CZ 9701962 | A3 | 19980114 (199810) | | |
| BR 9510521 | A | 19980714 (199835) | | |
| MX 9704733 | A1 | 19971001 (199901) | | |
| US 5861421 | A | 19990119 (199911) | | |
| KR 98700861 | A | 19980430 (199914) | | |
| NZ 301453 | A | 19990225 (199914) | | |
| HU 78042 | T | 19990628 (199931) | | |
| AU 708349 | B | 19990805 (199943) | | |
| CN 1175211 | A | 19980304 (200208) | | |
| JP 2002516601 | W | 20020604 (200239) | 90 | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9619995 | A1 | WO 1995-US16858 | 19951221 |
| ZA 9510884 | A | ZA 1995-10884 | 19951221 |
| AU 9646883 | A | AU 1996-46883 | 19951221 |
| NO 9702898 | A | WO 1995-US16858 | 19951221 |
| | | NO 1997-2898 | 19970620 |
| EP 800393 | A1 | EP 1995-944527 | 19951221 |
| | | WO 1995-US16858 | 19951221 |
| FI 9702673 | A | WO 1995-US16858 | 19951221 |
| | | FI 1997-2673 | 19970619 |
| CZ 9701962 | A3 | WO 1995-US16858 | 19951221 |
| | | CZ 1997-1962 | 19951221 |
| BR 9510521 | A | BR 1995-10521 | 19951221 |
| | | WO 1995-US16858 | 19951221 |
| MX 9704733 | A1 | MX 1997-4733 | 19970623 |
| US 5861421 | A | WO 1995-US16858 | 19951221 |
| | | US 1997-860404 | 19970623 |
| KR 98700861 | A | WO 1995-US16858 | 19951221 |
| | | KR 1997-704318 | 19970623 |
| NZ 301453 | A | NZ 1995-301453 | 19951221 |
| | | WO 1995-US16858 | 19951221 |
| HU 78042 | T | WO 1995-US16858 | 19951221 |
| | | HU 1998-2635 | 19951221 |
| AU 708349 | B | AU 1996-46883 | 19951221 |
| CN 1175211 | A | CN 1995-197681 | 19951221 |
| JP 2002516601 | W | WO 1995-US16858 | 19951221 |
| | | JP 1996-520574 | 19951221 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9646883 | A | Based on | WO 9619995 |
| EP 800393 | A1 | Based on | WO 9619995 |
| CZ 9701962 | A3 | Based on | WO 9619995 |
| BR 9510521 | A | Based on | WO 9619995 |
| US 5861421 | A | Based on | WO 9619995 |
| KR 98700861 | A | Based on | WO 9619995 |

| | | | |
|---|---|---|---|
| NZ 301453 | A | Based on | WO 9619995 |
| HU 78042 | T | Based on | WO 9619995 |
| AU 708349 | B | Previous Publ. | AU 9646883 |
| | | Based on | WO 9619995 |
| JP 2002516601 | W | Based on | WO 9619995 |

PRIORITY APPLN. INFO: US 1995-455796 19950531; US 1994-456234 19941223; US 1994-363130 19941223; US 1997-860404 19970623

AN 1996-321634 [32] WPIDS

AB WO 9619995 A UPAB: 19990412

phenyl-cyclohexane derivs. of formula (I) and (II), and salts of theseare new: R1 = QnC(O)OQmR6, QnC(O)NR4QmR6, QnOQmR6 or QrR6, in which alkyl moieties are opt. substd. by one or more F; m = 0-2; n = 0-4; r = 0-6; Q = CR4R5; R4,R5 = H or 1-2C alkyl; R6 = H, Me, OH, or aryl or aryloxy(1-3C)alkyl (both opt. substd. by halo); indanyl, indenyl, 7-11C polycycloalkyl, (tetrahydro)furanyl, (tetrahydro)pyranyl, (tetrahydro)thienyl, (tetrahydro)thiopyranyl, 3-6C cycloalkyl or 4-6C cycloalkyl contg. 1-2 unsatd. bonds, the cycloalkyl and heterocyclic moieties being opt. substd. by 1-3 Me, one Et or one OH; X = YR2, F, NR4R5 or formyl amine; Y = O, S, SO or SO2; X2 = O or NR8; R2 = Me or Et (both opt. substd. by one or more halo); s = 0-4; W = 2-6C alkyl, 2-6C alkenyl or 2-6C alkynyl; R3 = opt. substd. carboxy, amido or alkyl; Z = e.g. O, imino, oximo NCN; 2-(1,3-dithi(ol)ane), 2-(2,3-diox(ol)ane), 2-(1,3-oxathiolane), di(m)ethylthio ketal or di(m)ethyl ketal, Z' = e.g. opt. substd.2-,4- or 5-9 imidazolyl, 3-, 4- or 5-pyrazolyl, 4- or 5-triazolyl[1,2,3], 3- or 5-triazolyl[1,2,4], 5-tetrazolyl, 2-,4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 3- or 5-**oxadiazolyl**[1,2,4], 2-**oxadiazolyl**[1,3,4], 2-thiadiazolyl[1,3,4], 2-,4- or 5-thiazolyl, 2-, 4- or 5-oxazolidinyl, 2-, 4- or 5-thiazolidinyl or 2-, 4- or 5-imidazolidinyl; R8 = H or R9; R9 = 1-4C alkyl (opt. substd. by 1-3F).

USE - (I) and (II) inhibit phosphodiesterase IV (PDE IV) and prodn. of tumour necrosis factor (TNF). They are used for treatment or prophylaxis of PDE-IV- or TNF-mediated diseases, specifically: (i) allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivities, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxin shock and ARDS; (ii) diabetes insipidus and CNS disorders such as depression and multiinfarct dementia; (iii) viral infections, esp. infections by HIV, cytomegalovirus, influenza virus, adenovirus, **herpes** simplex, **herpes** zoster or animal viruses (e.g. FIV, equine infectious anaemia, caprine arthritis, visna or maedi virus), partic. HIV; and (iv) yeast and fungal infections, esp. fungal meningitis. (I) and (II) are also useful for reducing the toxicity of antifungal antibacterial or antiviral agents, specifically amphotericins, partic. amphotericin B.

ADVANTAGE - No further details.

Dwg.0/0

L17 ANSWER 11 OF 23 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 1996-321633 [32] WPIDS

DOC. NO. CPI: C1996-102370

TITLE: New 3-phenyl, 1,3-di substd. cyclohexane and cyclohexene cpds. - are useful in treatment of, e.g. asthma, ulcerative colitis, reperfusion injury, diabetes insipidus and viral infections.

DERWENT CLASS: B03 B05 C02 C03
INVENTOR(S): BENDER, P E; CHRISTENSEN, S B; KARPINSKI, J M; RYAN, M; RYAN, M D
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 19
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9619994 | A1 | 19960704 | (199632)* | EN | 24 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: JP US | | | | | |
| EP 796097 | A1 | 19970924 | (199743) | EN | |
| R: BE CH DE DK FR GB IT LI NL | | | | | |
| JP 10511397 | W | 19981104 | (199903) | | 33 |
| US 5869677 | A | 19990209 | (199913) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9619994 | A1 | WO 1995-US16839 | 19951221 |
| EP 796097 | A1 | EP 1995-944220 | 19951221 |
| | | WO 1995-US16839 | 19951221 |
| JP 10511397 | W | WO 1995-US16839 | 19951221 |
| | | JP 1996-520565 | 19951221 |
| US 5869677 | A | WO 1995-US16839 | 19951221 |
| | | US 1996-605167 | 19960227 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| EP 796097 | A1 | Based on | WO 9619994 |
| JP 10511397 | W | Based on | WO 9619994 |
| US 5869677 | A | Based on | WO 9619994 |

PRIORITY APPLN. INFO: US 1994-363664 19941223; US 1996-605167 19960227
AN 1996-321633 [32] WPIDS
AB WO 9619994 A UPAB: 19960819
Phenyl-cyclohexane derivs. of formulae (Ia), (Ib) and (Ic) and salts of these, are new: (Ia); (Ib); (Ic); R1 = QnC(O)O1QmR6, QnC(O)NR4QmR6, QnOQmR6 OR QrR6, in which alkyl moieties are opt. substd. by one or more halo; m = 0-2; n = 0-4; r = 0-6; Q = CR4R5; R4, R5 = H or 1-2C alkyl; R6 = H, Me, OH or aryl or aryloxyl(1-3C)alkyl (both opt. substd. by halo); indanyl, indenyl, 7-11C polycycloalkyl, (tetrahydro)furanyl, (tetrahydro)pyranyl, (tetrahydro)thienyl, (tetrahydro)thiopyranyl, 3-6C cycloalkyl or 4-6C cycloalkyl contg. 1-2 unsatd. bonds, the cycloalkyl and heterocyclic moieties being opt. substd. by 1-3 Me, one Et or one OH; X = YR2, F, NR4R5 or formyl amine; Y = O, SO or SO2; X2 = O or NR8; X3 = H or X; X4 = H, R9, OR8, CN, COR8, COOR8, CONR8R8 or NR8R8; R2 = Me or Et (both opt. substd. by one or more halo; s = 0-4; W = 2-6C alkyl, 2-6C alkenyl or 2-6C alkynyl; R3 = e.g substd. carboxy, amino or alkyl; Z = e.g. CN, or opt. substd. alcohol, thiol, ester, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-pyrazolyl, 4- or 5-triazolyl[1,2,3], 3- or 5-triazolyl[1,2,4], 5-tetrazolyl, 2-,4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 3- or 5-**oxadiazolyl**[1,2,4], 2-**oxadiazolyl**[1,3,4],

2-thiadiazolyl[1,3,4], 2-,4- or 5-thiazolyl, 2-,4- or 5-oxazolidinyl, 2-,4- or 5-thiazolidinyl or 2-, 4- or 5-imidazolidinyl.

USE - (I) inhibit phosphodiesterase IV (PDE IV) and prodn. of tumour necrosis factor (TNF). They are used for treatment or prophylaxis of PDE IV- or TNF-mediated diseases, specifically: (i) allergic and inflammatory diseases (claimed) including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivities, vernal conjunctivities, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxin shock and ARDS; (ii) diabetes insipidus and CNS disorders such as depression and multiinfarct dementia; (iii) viral infections, esp. infections by HIV, cytomegalovirus, influenza virus, adenovirus, **herpes** simplex, **herpes** zoster or animal viruses (e.g. FIV, equine infectious anaemia, caprine arthritis, visna or maedi virus), partic. HIV; and (iv) yeast and fungal infections, esp. fungal meningitis. (I) are also useful for reducing the toxicity of antifungal, antibacterial or antiviral agents, specifically amphotericins, partic. amphotericin B.

ADVANTAGE - No further details.

Dwg.0/0

L17 ANSWER 12 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-321632 [32] WPIDS
DOC. NO. CPI: C1996-102369
TITLE: New 1,3,3-tri substd. cyclohexene-1 cpds - are useful in treatment of, e.g. asthma, Crohn's disease, reperfusion injury, diabetes insipidus, fungal meningitis and viral infections.
DERWENT CLASS: B03 B05 C02 C03
INVENTOR(S): BENDER, P E; CHRISTENSEN, S B; KARPINSKI, J M; RYAN, M D
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 19
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9619993 | A1 | 19960704 | (199632)* | EN | 32 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: JP US | | | | | |
| US 5646158 | A | 19970708 | (199733) | | 13 |
| EP 801567 | A1 | 19971022 | (199747) | EN | |
| R: BE CH DE DK FR GB IT LI NL | | | | | |
| JP 10511660 | W | 19981110 | (199904) | | 42 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9619993 | A1 | WO 1995-US16713 | 19951221 |
| US 5646158 | A | WO 1995-US16713 | 19951221 |
| | | US 1996-605178 | 19960227 |
| EP 801567 | A1 | EP 1995-943944 | 19951221 |
| | | WO 1995-US16713 | 19951221 |
| JP 10511660 | W | WO 1995-US16713 | 19951221 |
| | | JP 1996-520531 | 19951221 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| US 5646158 | A | Based on | WO 9619993 |
| EP 801567 | A1 | Based on | WO 9619993 |
| JP 10511660 | W | Based on | WO 9619993 |

PRIORITY APPLN. INFO: US 1994-362728 19941223; US 1996-605178 19960227
AN 1996-321632 [32] WPIDS
AB WO 9619993 A UPAB: 19960819
phenyl-cyclohexene derivs. of formulae (Ia) and (Ib, and salts of these: (Ia); (Ib); R1 = QnC(O)OQmR6, QnC(O)NR4QmR6 or QrR6, in which alkyl moieties are opt. substd. by one or more halo; m = 0-2; n = 0-4; r = 0-6; Q = CR4R5; R4, R5 = H or 1-2C alkyl; R6 = H, Me, OH, or aryl or aryloxy (1-3C)alkyl (both opt. substd. by halo); indanyl, indenyl, 7-11C polycycloalkyl, (tetrahydro)furanyl, (tetrahydropyranyl, (tetrahydro)thienyl, (tetrahydro)thiopyranyl, 3-6C cycloalkyl or 4-6C cycloalkyl contg. 1-2 unsatd. bonds, the cycloalkyl and heterocyclic moieties being opt. substd. by 1-3 Me, one Et or one OH; X = YR2, F, NR4R5 or formyl amine; Y = O, S, SO or SO2; X2 = O or NR8; X3 = H or X; R2 = Me or Et (both opt. substd. by one or more halo); s = 0-4; W = 2-6C alkyl, 2-6C alkenyl or 2-6C alkynyl; R3 = COOR14, CONR4R14 or R15; Z = e.g. opt. substd amino, thio, sulphinyl orsulphonyl, amido, or ester; Z'=e.g. CN or opt. substd. ester or amide 2-, 4- or 5-imidazolyl, 3-, 4- or 5-pyrazolyl, 4- or 5-triazolyl[1,2,3], 3- or 5-triazolyl[1,2,4], 5-tetrazolyl, 2-,4- or 5-oxazolyl, 3- 4- or 5-isoxazolyl, 3- or 5-**oxadiazolyl**[1,2,4], 2-**oxadiazolyl**[1,3,4], 2-thiadiazolyl[1,3,4], 2-,4- or 5-thiazolyl, 2-,4- or 5-oxazolidinyl, 2-,4- or 5-thiazolidinyl or 2-, 4- or 5-imidazolidinyl

USE - (I) inhibit phosphodiesterase IV (PDE IV) and prodn. of tumour necrosis factor (TNF). They are used for treatment or prophylaxis of PDE-IV- or TNF-mediated diseases, specifically: (i) allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivities, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxin shock and ARDS; (ii) diabetes insipidus and CNS disorders such as depression and multiinfarct dementia; (iii) viral infections, esp. infections by HIV, cytomegalovirus, influenza virus, adenovirus, **herpes** simplex, **herpes** zoster or animal viruses (e.g. FIV, equine infectious anaemia, caprine arthritis, visna or maedi virus), partic. HIV; and (iv) yeast and fungal infections, esp. fungal meningitis. (I) are also useful for reducing the toxicity of antifungal antibacterial or antiviral agents, specifically amphotericins, partic. amphotericin B.

ADVANTAGE - No further details.

Dwg.0/0

ABEQ US 5646158 A UPAB: 19970813
A compound of Formula (Ia) or (Ib) wherein:

R1 is -(CR4R5)nC(O)O(CR4R5)mR6, -(CR4R5)nC(O)NR4(CR4R5)mR6, -(CR4R5)nO(CR4R5)mR6, or -(CR4R5)rR6 wherein the alkyl moieties are unsubstituted or substituted with one or more halogens; m is 0 to 2; n is 0 to 4; r is 0 to 6;

R4 and R5 are independently hydrogen or a C1-2 alkyl;

R6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC1-3 alkyl, halo substituted aryloxyC1-3 alkyl, indanyl, indenyl, C7-11 polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl,

C3-6 cycloalkyl, or a C4-6 cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl or heterocyclic moiety is optionally substituted by 1 to 3 methyl groups, one ethyl group or an hydroxyl group; provided that:

a) when R6 is hydroxyl, then m is 2; or

b) when R6 is hydroxyl, then r is 2 to 6; or

c) when R6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or d) when R6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6; e) when n is 1 and m is 0, then R6 is other than H in (CR4R5)nO(CR4R5)mR6; X is YR2, fluorine, NR4R5, or formyl amine; Y is O or S(O)m'; m' is 0, 1, or 2; X2 is O or NR8;

X3 is hydrogen or X; R2 is -CH3 or -CH2CH3 unsubstituted or substituted by 1 or more halogens; s is 0 to 4;

W is alkyl of 2 to 6 carbons, alkenyl of 2 to 6 carbons or alkynyl of 2 to 6 carbons; R3 is COOR14, C(O)NR4R14 or R15;

Z is S(O)m R9, OS(O)2R9, OR9, OC(O)NR7R7, OC(O)(O)qR7, O(CR4R5)nOR9, or NR9R9; q is 0 or 1; R7 is hydrogen or R9;

R8 is hydrogen or C1-4 alkyl unsubstituted or substituted by one to three fluorines, or when R8 and R10 are as -NR8R10 they together with the nitrogen form a a 5 to 7 membered ring comprised only of carbon atoms or carbon atoms and at least one heteroatom selected from O, N, or S; R9 is C1-10 alkyl, C2-10 alkenyl, C3-7cycloalkyl, C4-6 cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, each of which are optionally substituted by one or more fluorine atoms, or two R9 terms appearing as NR9R9 together with the nitrogen form a 5 to 7 membered ring comprised only of carbon atoms or carbon atoms and at least one heteroatom selected from O, N, or S;

R10 is OR8 or R8; R11 is C1-4 alkyl unsubstituted or substituted by one to three fluorines; R12 is R13, C3-C7 cycloalkyl, or an unsubstituted or substituted aryl or heteroaryl group selected from the group consisting of (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), quinolinyl, naphthyl, and phenyl;

R13 is a substituted or unsubstituted heteroaryl group selected from the group consisting of oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, **oxadiazolyl**, and thiadiazolyl, and where R13 is substituted on R12 or R13 the rings are connected through a carbon atom and each second R13 ring are optionally substituted by one or two C1-2 alkyl groups unsubstituted or substituted on the methyl with 1 to 3 fluoro atoms; R14 is hydrogen or R15; or when R10 and R14 are as NR10R14 they may together with the nitrogen form a 5 to 7 membered ring comprised only of carbon atoms or carbon atoms and at least one heteroatom selected from O, N, or S;

R15 is -(CR4R5)tR12 or C1-6 alkyl wherein the R12 or C1-6 alkyl group is unsubstituted or substituted by one or more times by methyl or ethyl unsubstituted or substituted by one to three fluorines, -F, -Br, -Cl, -NO2, -Si(R4)2, -NR8R10, -C(O)R8, -C(O)OR8, -O(CH2)qR8, -CN, -C(O)NR8R10, -O(CH2)qC(O)NR8R10, -O(CH2)qC(O)R10, -NR10C(O)NR8R10, -NR10C(O)R8, -NR10C(O)OR9, -NR10C(O)R13, -C(NR10)NR8R10, -C(NCN)NR8R10, -C(NCN)SR11, -NR10C(NCN)SR11, -NR10C(NCN)NR10R8, -NR10S(O)2R9, -S(O)m'R11, -NR10C(O)C(O)NR8R10, -NR10C(O)C(O)R10, or R13;

t is 0, 1, or 2; provided that:

f) when q is 1 in OC(O)(O)qR7, then R7 is not hydrogen;

g) R7 is not C1-4 alkyl unsubstituted or substituted by one to three fluorines; or the pharmaceutically acceptable salts thereof.

Dwg.0/0

L17 ANSWER 13 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-321629 [32] WPIDS
DOC. NO. CPI: C1996-102366
TITLE: New phenyl-cyclohexane and phenyl-cyclohexene cpds - are useful as phosphodiesterase IV inhibitors and inhibitors of tumour necrosis factor prodn.
DERWENT CLASS: B03 B05 C02 C03
INVENTOR(S): BENDER, P E; CHRISTENSEN, S B; KARPINSKI, J M; RYAN, M; RYAN, M D
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 19
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9619990 | A1 | 19960704 | (199632)* | EN | 31 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: JP US | | | | | |
| EP 796096 | A1 | 19970924 | (199743) | EN | |
| R: BE CH DE DK FR GB IT LI NL | | | | | |
| JP 10511398 | W | 19981104 | (199903) | | 41 |
| US 5863926 | A | 19990126 | (199911) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9619990 | A1 | WO 1995-US16857 | 19951221 |
| EP 796096 | A1 | EP 1995-944526 | 19951221 |
| | | WO 1995-US16857 | 19951221 |
| JP 10511398 | W | WO 1995-US16857 | 19951221 |
| | | JP 1996-520573 | 19951221 |
| US 5863926 | A | WO 1995-US16857 | 19951221 |
| | | US 1997-860401 | 19971006 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| EP 796096 | A1 | Based on | WO 9619990 |
| JP 10511398 | W | Based on | WO 9619990 |
| US 5863926 | A | Based on | WO 9619990 |

PRIORITY APPLN. INFO: US 1994-363123 19941223; US 1997-860401 19971006
AN 1996-321629 [32] WPIDS
AB WO 9619990 A UPAB: 19960819
Phenyl-cyclohexane derivs. of formulae (Ia) and (Ib), and salts of these, are new: (Ia); (Ib); R1 = QnC(O)OQmR6, QnC(O)NR4QmR6, QnOQmR6 or QrR6, in which alkyl moieties are opt. substd. by one or more F; m = 0-2; n = 0-4; r = 0-6; Q = CR4R5; R4,R5 = H or 1-2C alkyl; R6 = H, Me, OH, or aryl or aryloxy (1-3C) alkyl (both opt. substd. by halo); indanyl, indenyl, 7-11C polycycloalkyl, (tetrahydro)furanyl, (tetrahydro)pyranyl, (tetrahydro)thienyl, (tetrahydro)thiopyranyl, 3-6C cycloalkyl or 4-6C cycloalkyl contg. 1-2 unsatd. bonds, the cycloalkyl and heterocyclic moieties being opt. substd. by 1-3 Me, one Et or one OH; X = YR2 F, NR4R5 or formyl amine; Y = O, S, SO or SO2; X2 = O or NR8; X3 = H or X; X4 = H,

R9, OR8, CN, COR8, COOR8, CONR8R8 or NR8R8; R2 = Me or Et (both opt. substd. by one or more halo); R3 = COOR14, CONR4R14 or R7; s = 0-4; W = 2-6C alkyl, 2-6C alkenyl or 2-6C alkynyl; Z=e.g. opt. substd. thio, alcohol, ester carboxamide, 2-,4- or 5-imidazolyl, 3-, 4- or 5-pyrazolyl, 4- or 5-triazolyl[1,2,3], 3- or 5-triazolyl[1,2,4], 5-tetrazolyl, 2-,4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 3- or 5-**oxadiazolyl**[1,2,4], 2-**oxadiazolyl**[1,3,4], 2-thiadiazolyl[1,3,4], 2-,4- or 5-thiazolyl, 2-,4- or 5-oxazolidinyl, 2-, 4- or 5-thiazolidinyl or 2-, 4- or 5-imidazolidinyl; R8 = H or R9; R9 = 1-4C alkyl (opt. substd. by 1-3F);

USE - (I) inhibit phosphodiesterase IV (PDE IV) and prodn. of tumour necrosis factor (TNF). They are used for treatment or prophylaxis of PDE-IV- or TNF-mediated diseases, specifically: (i) allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivities, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxin shock and ARDS; (ii) diabetes insipidus and CNS disorders such as depression and multiinfarct dementia; (iii) viral infections, esp. infections by HIV, cytomegalovirus, influenza virus, adenovirus, **herpes** simplex, **herpes** zoster or animal viruses (e.g. FIV, equine infectious anaemia, caprine arthritis, visna or maedi virus), partic. HIV; and (iv) yeast and fungal infections, esp. fungal meningitis. (I) are also useful for reducing the toxicity of antifungal antibacterial or antiviral agents, specifically amphotericins, partic. amphotericin B.

ADVANTAGE - No further details.

Dwg.0/0

L17 ANSWER 14 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-321626 [32] WPIDS
DOC. NO. CPI: C1996-102363
TITLE: New 1,2 di substd. 4-phenyl-cyclohexane cpds - are useful as phosphodiesterase IV inhibitors and inhibitors of tumour necrosis factor prodn.
DERWENT CLASS: B03 B05 C02 C03
INVENTOR(S): BENDER, P E; CHRISTENSEN, S B; KARPINSKI, J M; RYAN, M D
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 19
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9619986 | A1 | 19960704 | (199632)* | EN | 23 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: JP US | | | | | |
| EP 794773 | A1 | 19970917 | (199742) | EN | |
| R: BE CH DE DK FR GB IT LI NL | | | | | |
| JP 10511659 | W | 19981110 | (199904) | | 32 |
| US 5990119 | A | 19991123 | (200002) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9619986 | A1 | WO 1995-US16712 | 19951221 |
| EP 794773 | A1 | EP 1995-943943 | 19951221 |
| | | WO 1995-US16712 | 19951221 |
| JP 10511659 | W | WO 1995-US16712 | 19951221 |

| | | | |
|---|---|---|---|
| | | JP 1996-520530 | 19951221 |
| US 5990119 | A | WO 1995-US16712 | 19951221 |
| | | US 1997-605033 | 19970623 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| EP 794773 | A1 | Based on | WO 9619986 |
| JP 10511659 | W | Based on | WO 9619986 |
| US 5990119 | A | Based on | WO 9619986 |

PRIORITY APPLN. INFO: US 1994-363668 19941223; US 1997-605033 19970623

AN 1996-321626 [32] WPIDS

AB WO 9619986 A UPAB: 19960819

Phenyl-cyclohexane derivs. of formula (I), and salts of (I), are new: (I); R1 = QnC(O)OQmR6, QnC(O)NR4QmR6, QnOQmR6 or Qrr6, in which alkyl moieties are opt. substd. by one or more F; m = 0-2; n = 0-4; r = 0-6; Q = CR4R5; R4,R5 = H or 1-2C alkyl; R6 = H, Me, OH or aryl or aryloxy (1-3C)alkyl (both opt. substd. by halo); indanyl, indenyl, 7-11C polycycloalkyl, (tetrahydro)furanyl, (tetrahydro)pyranyl, (tetrahydro)thienyl, (tetrahydro)thiopyranyl, 3-6C cycloalkyl or 4-6C cycloalkyl contg. 1-2 unsatd. bonds, the cycloalkyl and heterocyclic moieties being opt. substd. by 1-3 Me, one Et or one OH: W = 2-6C alkyl, 2-6C alkenyl or 2-6C alkynyl; X = YR2, halo, F, NR4R5 or formyl amine; Y = O, S, SO or SO2; X2 = O or NR8; X3 = H or X; R2 = Me or Et (both opt. substd. by one or more F); R3 = COOR14, CONR4R14 or R7; s = 0-4; Z = e.g. CR8R8V; V = CN, tetrazolyl, imidazolyl, imidazolidinyl, pyrazolyl, thiazolyl, thiazolidinyl, oxazolyl, oxazolidinyl, triazolyl, isoxazolyl, **oxadiazolyl**, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl or opt. substd. hydroxy, thiol, sulphinyl, sulphonyl, or amino; R8 = H or R9; R9 = 1-4C alkyl (opt. substd. by 1-3F)

USE - (I) inhibit phosphodiesterase IV (PDE IV) and prodn. of tumour necrosis factor (TNF). They are used for treatment or prophylaxis of PDE-IV- or TNF-mediated diseases, specifically: (i) allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivities, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxin shock and ARDS; (ii) diabetes insipidus and CNS disorders such as depression and multiinfarct dementia; (iii) viral infections, esp. infections by HIV, cytomegalovirus, influenza virus, adenovirus, **herpes** simplex, **herpes** zoster or animal viruses (e.g. FIV, equine infectious anaemia, caprine arthritis, visna or maedi virus), partic. HIV; and (iv) yeast and fungal infections, esp. fungal meningitis. (I) are also useful for reducing the toxicity of antifungal antibacterial or antiviral agents, specifically amphotericins, partic. amphotericin B.

ADVANTAGE - No further details.

Dwg.0/0

L17 ANSWER 15 OF 23 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 1996-321620 [32] WPIDS

DOC. NO. CPI: C1996-102357

TITLE: New bis-1-phenyl cyclohexyl-aliphatic hydrocarbon derivs. - used as TNF prodn. and phosphodiesterase inhibitors, e.g. for treating allergy, inflammation and viral or

fungal infections.
DERWENT CLASS: B05 C02 C03
INVENTOR(S): CHRISTENSEN, S B; KARPINSKI, J M
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 19
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9619980 | A1 | 19960704 | (199632)* | EN | 31 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: JP US | | | | | |
| EP 796092 | A1 | 19970924 | (199743) | EN | |
| R: BE CH DE DK FR GB IT LI NL | | | | | |
| JP 10511657 | W | 19981110 | (199904) | | 40 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9619980 | A1 | WO 1995-US16708 | 19951221 |
| EP 796092 | A1 | EP 1995-943940 | 19951221 |
| | | WO 1995-US16708 | 19951221 |
| JP 10511657 | W | WO 1995-US16708 | 19951221 |
| | | JP 1996-520526 | 19951221 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| EP 796092 | A1 | Based on | WO 9619980 |
| JP 10511657 | W | Based on | WO 9619980 |

PRIORITY APPLN. INFO: US 1994-363166 19941223
AN 1996-321620 [32] WPIDS
AB WO 9619980 A UPAB: 19960819
Bis-(3-Oxo-1-phenylcyclohexyl)-alkane, alkene or alkyne derivs. and analogues of formula (I) and their salts are new.Z1 = Z and Z2 = H, i.e. cpds. (I'); or Z1 = O and Z2 = Z', i.e. cpds. (I''); R1 = -(CR4R5)nCOO(CR4R5)mR6, -(CR4R5)nCONR4(CR4R5)mR6, -(CR4R5)nO(CR4R5)mR6 or -(CR4R5)rR6, where alkyl moieties are opt. substd. by one or more F; m = 0-2; n = 0-4; r = 0-6; R4, R5 = H, Me or Et; R6 = H, Me, OH, opt. halo substd. aryl, opt. halo substd. aryloxy-(1-3C)alkyl, indanyl, indenyl, 7-11C polycycloalkyl, furanyl, pyranyl, thienyl, thiopyranyl (the last four opt. as tetrahydro derivs.), 3-6C cycloalkyl, 4-6C cycloalkyl contg. 1 or 2 unsatd. bonds, where cycloalkyl or heterocyclic moieties are opt. substd. by 1-3 Me, one Et or one OH; provided that (a) if R6 = OH, then m = 2 or r = 2-6, (b) if R6 = 2-tetrahydro(pyranyl, thiopyranyl, furanyl or thienyl), then m = 1 or 2 or r = 1-6 or (c) if n = 1 and m = 0, then R6 is other than H in -(CR4R5)nO(CR4R5)mR6; W = 2-6C alkylene, 2-6C alkenylene or 2-6C alkynylene; X = YR2, F, NR4R5 or NCONH : Y = O or S(O)m'; m' = 0-2; X2 = O or NR8; X3 = H or X; R2 = methyl or ethyl (both opt. substd. by one or more F); s = 0-4; Z= e.g O, imino, opt. substd. oxime, NCN, C(CN)OCOR9, C(CN)OR9, 2-(1,3-dithiane), 2-(1,3-dithiolane), dimethylthio ketal, diethylthio ketal, 2-(1,3-dioxolane), 2-(1,3-dioxan), 2-(1,3-oxathiolane), dimethyl ketal or diethyl ketal; Z' = e.g opt. substd alcohol, thio, amido, C(NCN)SR9, imidazol-2-, 4- or 5-yl, pyrazolyl, 1,2,3-triazol-4- or 5-yl, 1,2,4-triazol-3- or 5-yl, 5-tetrazolyl,

oxazolyl, isoxazolyl, 1,2,4-**oxadiazolyl**, 1,3,4-**oxadiazolyl**, 1,3,4-thiadiazolyl, thiazolyl, oxazolidin-2-,4- or 5-yl, thiazolidin-2, 4- or 5-yl or imidazolidin-2-, 4- or 5-yl, R8 = H or R9; R9 = 1-4C alkyl (opt. substd. by 1-3 F)

USE - (I) inhibit phosphodiesterase IV (PDE IV) and prodn. of tumour necrosis factor (TNF). They are used for treatment or prophylaxis of PDE IV- or TNF-mediated diseases, specifically: (i) allergic and inflammatory diseases (claimed) including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivities, vernal conjunctivities, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxin shock and ARDS; (ii) diabetes insipidus and CNS disorders such as depression and multiinfarct dementia; (iii) viral infections, esp. infections by HIV, cytomegalovirus, influenza virus, adenovirus, **herpes** simplex, **herpes** zoster or animal viruses (e.g. FIV, equine infectious anaemia, caprine arthritis, visna or maedi virus), partic. HIV; and (iv) yeast and fungal infections, esp. fungal meningitis. (I) are also useful for reducing the toxicity of antifungal, antibacterial or antiviral agents, specifically amphotericins, partic. amphotericin B.

Dwg.0/0

L17 ANSWER 16 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-321618 [32] WPIDS
DOC. NO. CPI: C1996-102355
TITLE: New bis-1-phenyl cyclohexenyl-aliphatic hydrocarbon derivs. - used as TNF prodn. and phosphodiesterase inhibitors, e.g. for treating allergy, inflammation or viral or fungal infections.
DERWENT CLASS: B05 C02 C03
INVENTOR(S): CHRISTENSEN, S B; KARPINSKI, J M
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 19
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9619978 | A1 | 19960704 | (199632)* | EN | 28 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: JP US | | | | | |
| EP 841908 | A1 | 19980520 | (199824) | EN | |
| R: BE CH DE DK FR GB IT LI NL | | | | | |
| US 5795918 | A | 19980818 | (199840) | | |
| JP 10511661 | W | 19981110 | (199904) | | 37 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9619978 | A1 | WO 1995-US16714 | 19951221 |
| EP 841908 | A1 | EP 1995-943945 | 19951221 |
| | | WO 1995-US16714 | 19951221 |
| US 5795918 | A | WO 1995-US16714 | 19951221 |
| | | US 1996-605182 | 19960227 |
| JP 10511661 | W | WO 1995-US16714 | 19951221 |
| | | JP 1996-520532 | 19951221 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| EP 841908 | A1 | Based on | WO 9619978 |
| US 5795918 | A | Based on | WO 9619978 |
| JP 10511661 | W | Based on | WO 9619978 |

PRIORITY APPLN. INFO: US 1994-362709 19941223; US 1996-605182 19960227
AN 1996-321618 [32] WPIDS
AB WO 9619978 A UPAB: 19960819
Bis-(1-phenyl-3-substd. or 3,4-disubstd. cyclohex-2- or 3-enyl)alkane, alkene or alkyne derivs. of formula (I), and their salts are new.Z1 - Z, Z2 = H and a 3(4)-double bond is present, i.e. cpds. (I'); Z1 = Z, Z2 = H an a 2(3)-double bond is present, i.e. cpds. (I''); or Z1 = Z'', Z2 = Z' and a 3(4)-double bond is present, i.e. cpds. (I'''); R1 = -(CR4R5)nCOO(CR4R5)mR6, -(CR4R5)nCONR4(CR4R5)mR6, -CR4R5)nO(CR4R5)mR6 or -(CR4R5)rR6, where alkyl moieties are opt. substd. by halogen(s); m = 0-2; n = 0-4; r = 0-6; R4,R5 = H, Me or Et; R4,R5 = H, Me or Et; R6 = H, Me, OH, opt. halo substd. aryl, opt. halo substd. aryloxy-(1-3C)alkyl, indanyl, indenyl, 7-11C polycycloalkyl, furanyl, thienyl, pyranyl, thiopyranyl (the last four opt. as tetrahydro derivs.), 3-6C cycloalkyl or 4-6C cycloalkyl contg. 1 or 2 unsatd. bonds, where cycloalkyl and heterocyclic moieties are opt. substd. by 1-3 Me, one Et one OH; provided that (a) if R6 = OH, then m = 2 or r = 2-6, (b) if R6 = 2-tetrahydro(pyranyl, thiopyranyl, thienyl or furanyl, then m = 1 or 2 or r = 1-6 or (c) if n = 1 and m = 0, then R6 is other than H in (CR4R5)nO(CR4R5)mR6; X = YR2, F, NR4R5 or HCONH; Y = 0 or S(O)m; m' = 0-2; X2 = 0 or NR8; X3 = H or X; R2 = methyl or ethyl, both opt. substd. by halogen(s); s = 0-4; W = 2-6C alkylene, 2-6C alkenylene or 2-6C alkynylene; Z, Z'' = e.g. S(O)m,R9, OSO2R9, OR9 or opt. substd. amino; Z' = e.g. CN, or opt. substd. 2-, 4- or 5-imidazolyl, pyrazolyl, 1,2,3-triazol-4- or 5-yl, 1,2,4-triazol-3- or 5-yl, 5-tetrazolyl, oxazolyl, isoxazolyl, 1,2,4- or 1,3,4-**oxadiazolyl**, 1,3,4-thiadiazolyl, thiazolyl, 2-, 4- or 5-oxazolidinyl, 2-, 4- or 5-thiazolidinyl or 2-, 4- or 5- imidazolidinyl, ester or carbamide.

USE - (I) inhibit phosphodiesterase IV (PDE) IV and prodn. of tumour necrosis factor (TNF). They are used for treatment or prophylaxis of PDE IV- or TNF-mediated diseases, specifically: (i) allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivities, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxin shock and ARDS; (ii) diabetes insipidus and CNS disorders such as depression and multiinfarct dementia; (iii) viral infections, esp. infections by HIV, cytomegalovirus, influenza virus, adenovirus, **herpes** simplex, **herpes** zoster or animal viruses (e.g. FIV, equine infectious anaemia, caprine arthritis, visna or maedi virus) partic. HIV; and (iv) yeast and fungal infections, esp. fungal meningitis. (I) are also useful for reducing the toxicity of antifungal, antibacterial or antiviral agents, specifically amphotericins, partic. amphotericin B.
Dwg.0/0

L17 ANSWER 17 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1995-373541 [48] WPIDS
DOC. NO. CPI: C1995-161823
TITLE: New substd. bi phenyl derivs. - are phosphodiesterase IV

and TNF inhibitors.
DERWENT CLASS: B05
INVENTOR(S): BENDER, P E; CHRISTENSEN, S B
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 18
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9527692 | A1 | 19951019 | (199548)* | EN | 4 |

RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: JP US

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9527692 | A1 | WO 1995-US4294 | 19950407 |

PRIORITY APPLN. INFO: US 1994-225118 19940408
AN 1995-373541 [48] WPIDS
AB WO 9527692 A UPAB: 19951204
Substituted biphenyl derivs. of formula (I) and their salts are new. R1 = (CR4R5)nC(=O)O(CR4R5)mR6, (CR4R5)nC(=O)NR4(CR4R5)mR6, (CR4R5)nO(CR4R5)mR6 or (CR4R5)rR6 (where each alkyl moiety is opt. substd. by halo); R2 = Me or Et (both opt. halogenated); R4, R5 = H, Me or Et; R6 = H, Me, OH, aryl, haloaryl, aryloxy1-3Calkyl, (opt. halogenated); or indanyl, indenyl, 7-11C polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, 3-6C cycloalkyl or 4-6C cycloalkyl contg. 1-2 unsaturated bonds (all opt. substd. by 1-3 Me, 1 Et or 1 OH gp.); R7 = (CR4R5)qR12 or 1-6C alkyl where R12 or 1-6C alkyl are opt. substd. by 1-2C alkyl (opt. substd. by 1-3Q); Q = F, Br, Cl, NO2, NR10R11, C(=O)R8, C(=O)OR8, OR8, CN, C(=O)NR10R11, OC(=O)NR10R11, OC(=O)R8, NR10C(=O)NR10R11, NR10C(=O)R11, NR10C(=O)OR9, NR10C(=O)R13, C(=NR10)NR10R11, C(=N-CN)NR10R11, C(=N-CN)SR9, NR10C(=N-CN)NR10R11, NR10S(=O)2R9, -S(=O)mR9, NR10C(=O)C(=O)NR10R11, NR10C(=O)C(=O)R10 or R13; R8 = H or R9; R9, R11 = 1-4C alkyl (opt. substd. by 1-3 F); R10 = OR8 or R11; or NR10R11 = 5-7 membered ring contg. an additional O, N or S; R12 = 3-7C cycloalkyl, 2, 3 or 4-pyridyl, pyrimidyl, pyrazolyl, 1- or 2-imidazolyl, thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, 2- or 3-thienyl, 4- or 5-thiazolyl, quinolinyl, naphthyl or phenyl; R13 = oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, **oxadiazolyl** or thiadiazolyl (all attached via C and opt. substd. by 1-2 of Me and/or Et); R14 = H or R7; or NR10R14 = 5-7 membered ring contg. at least one additional N, O or S; m, m' = 0-2; n = 1-4; r = 0-6; q = 0-2; X1 = YR6, halo, NO2, NR4R5 or formylamino; X2 = O or NR8; X3 = H or X1; Y = O or S(O)m'; Y' = O or S; Z, Z2, Z3 = H, (CH2)pCN, (CH2)pCO2R14, C(=O)H, C(=NR10)NR10R14, C(=NOR8)R14, C(=O)NR8NR8C(=O)R8, C(=O)NR8NR10R14, C(=NOR14)R8, C(=NR8)NR10R14, C(=NR14)NR8R8, C(=N-CN)NR10R14, C(=N-CN)SR9, 2, 4 or 5-imidazolyl, 3, 4 or 5-pyrazolyl, 4 or 5-triazolyl(1,2,3), 3 or 5-triazolyl(1,2,4), 5-tetrazolyl, 2, 4 or 5-oxazolyl, 3, 4 or 5-isoxazolyl, 3 or 5-**oxadiazolyl**(1,2,4), 2-**oxadiazolyl**(1,3,4), 2-thiadiazolyl(1,3,4), 5-thiadiazolyl(1,2,4), 2, 4 or 5-thiazolyl, 2, or 5-oxazolidinyl, 2, 4 or 5-thiazolidinyl, 2, 4 or 5-imidazolidinyl (all opt. substd. by R14); Z1 = H, OH, CN, CO2H, CO2Me or CONH2; p = 1-3; with

provisos. N.B. R2 and Y' do not appear in any formulae.

USE - (I) are TNF inhibitors and phosphodiesterase IV catalytic activity inhibitors used to treat allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, ARDS, diabetes insipidus, CNS disorders such as depression and multi-infarct dementia, viruses, e.g. HIV-1, HIV-2, HIV-3, CMV, influenza, adenovirus and **herpes** viruses, e.g. **Herpes** zoster and **Herpes** simplex etc..

Dwg.0/0

L17 ANSWER 18 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1995-090571 [12] WPIDS
DOC. NO. CPI: C1995-040944
TITLE: New cyclohexyl or cyclohexenyl substd. phenyl cpds. inhibit TNF prodn and phosphodiesterase IV - used to treat e.g. inflammatory and allergic diseases, diabetes insipidus, CNS conditions, viral and fungal infections, etc..
DERWENT CLASS: B03 B05
INVENTOR(S): CHRISTENSEN, S B; FORSTER, C J
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 48
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9503794 | A1 | 19950209 | (199512)* | EN | 40 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE | | | | | |
| W: AU BB BG BR BY CA CN CZ FI HU JP KP KR KZ LK MG MN MW NO NZ PL RO RU SD SI SK UA US VN | | | | | |
| AU 9473751 | A | 19950228 | (199522) | | |
| ZA 9405643 | A | 19950426 | (199523) | | 37 |
| EP 714293 | A1 | 19960605 | (199627) | EN | |
| R: BE CH DE FR GB IT LI NL | | | | | |
| JP 09501420 | W | 19970210 | (199716) | | 61 |
| US 6300372 | B1 | 20011009 | (200162) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9503794 | A1 | WO 1994-US8581 | 19940729 |
| AU 9473751 | A | AU 1994-73751 | 19940729 |
| ZA 9405643 | A | ZA 1994-5643 | 19940729 |
| EP 714293 | A1 | EP 1994-922761 | 19940729 |
| | | WO 1994-US8581 | 19940729 |
| JP 09501420 | W | WO 1994-US8581 | 19940729 |
| | | JP 1995-505999 | 19940729 |
| US 6300372 | B1 | WO 1994-US8581 | 19940729 |
| | | US 1996-586770 | 19960130 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---|---|---|

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| | | | |
|---|---|---|---|
| AU 9473751 | A | Based on | WO 9503794 |
| EP 714293 | A1 | Based on | WO 9503794 |
| JP 09501420 | W | Based on | WO 9503794 |
| US 6300372 | B1 | Based on | WO 9503794 |

PRIORITY APPLN. INFO: US 1993-130214 19931001; US 1993-99900 19930730; US 1996-586770 19960130

AN 1995-090571 [12] WPIDS

AB WO 9503794 A UPAB: 19950328

Cyclohexyl or cyclohexenyl substd. phenyl cpds. of formula (I) and their salts are new.

R1 = -(CR4R5)nC(O)O(CR4R5)mR6, -(CR4R5)nC(O)NR4(CR4R5)mR6, -(CR4R5)nO(CR4R5)mR6 or -(CR4R5)rR6 where the alkyl moieties are opt. substd. by halo;

m = 0-2;

n = 1-4;

r = 0-6;

R4, R5 = H or 1-2C alkyl;

R6 = H, Me, OH, aryl opt. substd. by halo, aryloxy(1-3C)alkyl opt. substd. by halo, indanyl, indenyl, 7-11C polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, 3-6C cycloalkyl or 4-6C cycloalkenyl contg. 1 or 2 unsatd. bonds, where the cycloalkyl or heterocyclic gps. are opt. substd. by 1-3 Me or one Et;

provided that: (i) when R6 = OH, m = 2; or (ii) when R6 = OH, r = 2-6; or (iii) when R6 = 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl or 2-tetrahydrothienyl, m = 1 or 2, or r = 1-6; (iv) when n = 1 and m = 0, R6 is not H in -(CR4R5)nO(CR4R5)mR6;

X = YR2, halo, NO2, NR4R5 or formylamine;

Y = O or S(O)m';

m' = 0-2;

X2 = O or NR8;

X3 = H or X;

X4 = gp. (i) or (ii);

X5 = H, R9, OR8, CN, C(O)R8, C(O)OR8, C(O)N(R8)2 or N(R8)2;

R2 = CH3 or CH2CH3 opt. substd. by halo;

s = 0-4;

R3 = H, halo, 1-4C alkyl opt. substd. by halo, CH2NHC(O)C(O)NH2;

Z = CN, C(O)NR8NR8C(O)R8, C(NCN)SR9, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-pyrazolyl, 4- or 5-(1,2,3)triazolyl, 3- or 5-(1,2,4)triazolyl, 5-tetrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 3- or 5-(1,2,4)**oxadiazolyl**, 2-(1,3,4)**oxadiazolyl**, 2-(1,3,4)thiadiazolyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-oxazolidinyl, 2-, 4- or 5-thiazolidinyl or 2-, 4- or 5-imidazolidinyl wherein all heterocycles are opt. substd.;

R8 = H or R9;

R9 = 1-4C alkyl opt. substd. by 1-3 F.

USE - Cpds. (I) have tumour necrosis factor (TNF) and phosphodiesterase IV (PDE IV) inhibitory activity. PDE IV inhibitors are used to treat various allergic and inflammatory diseases, diabetes insipidus and CNS disorders. (I) are also useful in treating viruses which are sensitive to upregulation by TNF or will elicit TNF prodn. in vivo. Such viruses include HIV-1, HIV-2, HIV-3, cytomegalovirus, influenza, adenovirus and **Herpes** viruses. (I) may also be used to treat viral infections in animals, and fungal and yeast infections affected by TNF prodn. e.g., fungal meningitis. (I) may be co-administered with other antifungal cpds., and also used to reduce the toxicity of another

anti-fungal, anti-bacterial or anti-viral agents.
Dwg.0/0

L17 ANSWER 19 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1995-036375 [05] WPIDS
CROSS REFERENCE: 1997-362977 [33]; 1998-167941 [15]; 2000-205222 [18]; 2002-711569 [77]
DOC. NO. CPI: C1995-016309
TITLE: New antitumour, antiviral Lavendamycin analogues - active against breast, colon tumours, parasitic infections, retroviruses, etc..
DERWENT CLASS: B03 C02
INVENTOR(S): BEHFOROUZ, M; MERRIMAN, R L
PATENT ASSIGNEE(S): (BEHF-I) BEHFOROUZ M; (MERR-I) MERRIMAN R L
COUNTRY COUNT: 54
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9429308 | A1 | 19941222 | (199505)* | EN | 103 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE | | | | | |
| W: AT AU BB BG BR BY CA CH CN CZ DE DK ES FI GB GE HU JP KG KP KR KZ LK LU LV MD MG MN MW NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA UZ VN | | | | | |
| AU 9472440 | A | 19950103 | (199521) | | |
| EP 701557 | A1 | 19960320 | (199616) | EN | |
| R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE | | | | | |
| US 5525611 | A | 19960611 | (199629) | | 27 |
| JP 09501412 | W | 19970210 | (199716) | | 95 |
| EP 701557 | A4 | 19970709 | (199813) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9429308 | A1 | WO 1994-US6150 | 19940531 |
| AU 9472440 | A | AU 1994-72440 | 19940531 |
| EP 701557 | A1 | EP 1994-921922 | 19940531 |
| | | WO 1994-US6150 | 19940531 |
| US 5525611 | A | US 1993-71648 | 19930604 |
| JP 09501412 | W | WO 1994-US6150 | 19940531 |
| | | JP 1995-501909 | 19940531 |
| EP 701557 | A4 | EP 1994-921922 | 19940531 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9472440 | A | Based on | WO 9429308 |
| EP 701557 | A1 | Based on | WO 9429308 |
| JP 09501412 | W | Based on | WO 9429308 |

PRIORITY APPLN. INFO: US 1993-71648 19930604
AN 1995-036375 [05] WPIDS
CR 1997-362977 [33]; 1998-167941 [15]; 2000-205222 [18]; 2002-711569 [77]
AB WO 9429308 A UPAB: 20021204
Lavendamycin analogues of formula (I) and their salts are new. X = R10CONH or R10CSNH; Y = H, OR11, SR11, N(R11)2, NR11N(R11)2, halo, NO2, CN,

R11C(=NR11), R12CO, R12CS or alkyl, aryl, cycloalkyl, alkynyl, alkenyl or heterocyclyl (all opt. substd.); R1 - R8 = H, halo, NO2, CN, OR13, SR13, N(R13)2, CON(R13)2, CSN(R13)2, COR13, CSR13, C(=NR13)R13 or alkyl, aryl, cycloalkyl, alkenyl, alkynyl or heteroalkyl, heterocyclyl, heteroalkenyl or heteroalkynyl (all opt. substd.); R9 = H, R12CO, R12CS or alkyl, cycloalkyl, aryl, alkenyl, alkynyl or heterocyclyl (all opt. substd.); R10, R11, R13 = H or alkyl, cycloalkyl, alkenyl, alkynyl, aryl or heterocyclyl (all opt. substd.); R12 = H, N(R11)2, OR11, SR11, NR11N(R11)2, OR14N(R11)2 or alkyl, cycloalkyl, aryl, alkenyl, alkynyl or heterocyclyl (all opt. substd.); and R14 = alkylene.

USE - (I) are useful as antitumour, antibacterial, antiviral and antiparasitic agents. They can be used to treat bacterial infections caused by both gram-positive and gram-negative bacteria such as Staphylococcus, Listerella, Sa,monella and Mycobacterium. (I) are active against retroviruses such as HIV-1 and HIV-2, **herpes** viruses, hepadna viruses, picorna viruses and pox viruses. (I) treat parasitic infections such as those caused by Amoeba, Babesia and Nosema. (I) are active against ovarian, colon, breast, stomach, pancreatic and skin tumours. In partic. (I) have been found to be selectively active against ras K tumour cells.

Dwg.0/0

ABEQ US 5525611 A UPAB: 19960724

A compound having the following formula (I), wherein, X is R10OCNH or R10SCNH, Y is H, OR11 SR11, N(R11)2, NR11N(R11)2, a halogen atom, NO2, CN, R11C(=NR11), R12CO, R12CS, or an alkyl, aryl, cycloalkyl, alkynyl, alkenyl or heterocyclic residue, said heterocyclic residue being selected from the group consisting of thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isothiazolyl, is oxazolyl, thiazolyl, **oxadiazolyl**, and thiadiazolyl, each of said residues is unsubstituted or substituted with a single substituent selected from the group consisting of Rx, NH2, RxNH (Rx)2N, CN, N3, NO2, OH, halogen, SH, RxS, RxSO2, RxSO, RxO, COOH, COORx, CORx, CHO and CON (Rx)2, R4 and R6, which may be the same or different, each is independently H, a halogen atom, NO2, CN, OR13, SR13, N(R13)2, -C(=O)N(R13)2, C(=S)N(R13)2, C(=O)R13, C(=S)R13, C(=NR13)R13, an alkyl, aryl, cycloalkyl, alkenyl, alkynyl, or heterocyclic residue, said-alkyl residue optionally containing a heteroatom selected from the group consisting of oxygen, sulphur and nitrogen, said heterocyclic residue being selected from the group consisting of thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isothiazolyl, isoxazolyl, thiazolyl, **oxadiazolyl**, and thiadiazolyl, each of said residues is unsubstituted or substituted with a single substituent selected from the group consisting of Rx, NH2, RxNH, (Rx)2N, CN, N3, NO2, OH, halogen, SH, RxS, RxSO2, RxSO, RxO, COOH, COORx, CORx, CHO and CON(Rx)2, R10, R11 and R13 which is the same or different, each is independently H or an alkyl, cycloalkyl, alkenyl, alkynyl, aryl or heterocyclic residue, said heterocyclic residue being selected from the group consisting of thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isothiazolyl, isoxazolyl, thiazolyl, **oxadiazolyl**, and thiadiazolyl, each of said residues is unsubstituted or substituted with a single substituent selected from the group consisting of Rx, NH2, RxNH, (Rx)2N, CN, N3, NO2, OH, halogen, SH, RxS, RxSO2, RxSO, RxO, COOH, COORx, CORx, CHO and CON(Rx)2, R12 is H, N(R11)2, OR11, SR11, NR11N (R11)2, OR14N(R11)2, or an alkyl, cycloalkyl, aryl, alkenyl, alkynyl or heterocyclic residue, said heterocyclic residue being selected from the group consisting of thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isothiazolyl, isoxazolyl, thiazolyl,

**oxadiazolyl**, and thiadiazolyl, each of said residues are unsubstituted or substituted with a single substituent selected from the group consisting of Rx, NH2, RxNH, (Rx)2N, CN, N3, NO2, OH, halogen, SH RxS, RxSO2, RxSO, RxO, COOH, COORx, CORx, CHO and CON(Rx)2, and R14 is an alkylene residue, Rx is an alkyl, cycloalkyl, aryl, alkenyl, alkynyl or heterocyclic residue, said heterocyclic residue being selected from the group consisting of thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isothiazolyl, isoxazolyl, thiazolyl, **oxadiazolyl**, and thiadiazolyl,
or a pharmaceutically acceptable salt thereof.
Dwg.0/0

L17 ANSWER 20 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1993-336568 [42] WPIDS
CROSS REFERENCE: 1997-131824 [12]
DOC. NO. CPI: C1993-148850
TITLE: New phenyl derivs. - useful as phosphodiesterase IV and tumour necrosis factor inhibitors.
DERWENT CLASS: B03 B05 C02 C03
INVENTOR(S): CHRISTENSEN, S B; CHRISTENSEN, I S B
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 48
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9319749 | A1 | 19931014 | (199342)* | EN | 45 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LI LU MC MW NL OA PT RU SD SE | | | | | |
| W: AU BB BG BR CA CZ FI HU JP KP KR LK MG MN NO NZ PL RO SK US | | | | | |
| ZA 9302264 | A | 19931124 | (199402) | | 44 |
| AU 9337910 | A | 19931108 | (199408) | | |
| NO 9403663 | A | 19941115 | (199505) | | |
| EP 633776 | A1 | 19950118 | (199507) | EN | |
| R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE | | | | | |
| FI 9404549 | A | 19941130 | (199508) | | |
| CZ 9402397 | A3 | 19950517 | (199528) | | |
| SK 9401171 | A3 | 19950607 | (199532) | | |
| EP 633776 | A4 | 19950125 | (199546) | | |
| JP 07508508 | W | 19950921 | (199546) | | 18 |
| US 5552438 | A | 19960903 | (199641) | | 18 |
| NZ 251092 | A | 19961220 | (199708) | | |
| CN 1092406 | A | 19940921 | (199716) | | |
| TW 294652 | A | 19970101 | (199716) | | |
| US 5614540 | A | 19970325 | (199720) | | |
| AU 677776 | B | 19970508 | (199727) | | |
| HU 70523 | T | 19951030 | (199732) | | |
| US 5643946 | A | 19970701 | (199732) | | 17 |
| AU 9733229 | A | 19971023 | (199750) | | |
| SG 47107 | A1 | 19980320 | (199818)# | | |
| CZ 283425 | B6 | 19980415 | (199821) | | |
| BR 1100473 | A3 | 19980422 | (199822) | | |
| NO 303116 | B1 | 19980602 | (199828) | | |
| JP 2873090 | B2 | 19990324 | (199917) | | 26 |
| EP 919544 | A1 | 19990602 | (199926) | EN | |
| R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE | | | | | |
| SK 279958 | B6 | 19990611 | (199930) | | |
| AU 705566 | B | 19990527 | (199932) | | |
| MX 187418 | B | 19971210 | (199936) | | |

AU 9936759 A 19990819 (199945)
IL 105221 A 20000131 (200015)
RU 2136656 C1 19990910 (200035)
AU 724115 B 20000914 (200051)
RO 115872 B1 20000728 (200052)
EP 633776 B1 20010509 (200128) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
DE 69330206 E 20010613 (200141)
ES 2157923 T3 20010901 (200161)
PH 31379 A 19981029 (200254)

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| WO 9319749 | A1 | | WO 1993-US1991 | 19930305 |
| ZA 9302264 | A | | ZA 1993-2264 | 19930330 |
| AU 9337910 | A | | AU 1993-37910 | 19930305 |
| NO 9403663 | A | | WO 1993-US1991 | 19930305 |
| | | | NO 1994-3663 | 19940930 |
| EP 633776 | A1 | | EP 1993-907233 | 19930305 |
| | | | WO 1993-US1991 | 19930305 |
| FI 9404549 | A | | WO 1993-US1991 | 19930305 |
| | | | FI 1994-4549 | 19940930 |
| CZ 9402397 | A3 | | CZ 1994-2397 | 19930305 |
| SK 9401171 | A3 | | WO 1993-US1991 | 19930305 |
| | | | SK 1994-1171 | 19930305 |
| EP 633776 | A4 | | EP 1993-907233 | |
| JP 07508508 | W | | JP 1993-517446 | 19930305 |
| | | | WO 1993-US1991 | 19930305 |
| US 5552438 | A | CIP of | US 1992-862030 | 19920402 |
| | | CIP of | US 1992-968762 | 19921030 |
| | | | WO 1993-US1991 | 19930305 |
| | | | US 1994-313094 | 19940929 |
| NZ 251092 | A | | NZ 1993-251092 | 19930305 |
| | | | WO 1993-US1991 | 19930305 |
| CN 1092406 | A | | CN 1993-105725 | 19930402 |
| TW 294652 | A | | TW 1993-104962 | 19930622 |
| US 5614540 | A | CIP of | US 1992-862030 | 19920402 |
| | | CIP of | US 1992-968762 | 19921030 |
| | | CIP of | WO 1993-US1991 | 19930305 |
| | | Cont of | US 1994-313094 | 19940929 |
| | | | US 1995-457942 | 19950518 |
| AU 677776 | B | | AU 1993-37910 | 19930305 |
| HU 70523 | T | | WO 1993-US1991 | 19930305 |
| | | | HU 1994-2817 | 19930305 |
| US 5643946 | A | CIP of | US 1992-862030 | 19920402 |
| | | CIP of | US 1992-968762 | 19921030 |
| | | Cont of | WO 1993-US1991 | 19930305 |
| | | Cont of | US 1994-313094 | 19940929 |
| | | | US 1995-443636 | 19950518 |
| AU 9733229 | A | Div ex | AU 1993-37910 | 19930305 |
| | | | AU 1997-33229 | 19970808 |
| SG 47107 | A1 | | SG 1996-7903 | 19930305 |
| CZ 283425 | B6 | | WO 1993-US1991 | 19930305 |
| | | | CZ 1994-2397 | 19930305 |
| BR 1100473 | A3 | | BR 1997-1100473 | 19970505 |
| NO 303116 | B1 | | WO 1993-US1991 | 19930305 |

| | | | | |
|---|---|---|---|---|
| | | | NO 1994-3663 | 19940930 |
| JP 2873090 | B2 | | JP 1993-517446 | 19930305 |
| | | | WO 1993-US1991 | 19930305 |
| EP 919544 | A1 | Div ex | EP 1993-907233 | 19930305 |
| | | | EP 1998-204466 | 19930305 |
| SK 279958 | B6 | | WO 1993-US1991 | 19930305 |
| | | | SK 1994-1171 | 19930305 |
| AU 705566 | B | Div ex | AU 1993-37910 | 19930305 |
| | | | AU 1997-33229 | 19970808 |
| MX 187418 | B | | MX 1993-1943 | 19930402 |
| AU 9936759 | A | Div ex | AU 1997-33229 | 19970808 |
| | | | AU 1999-36759 | 19990624 |
| IL 105221 | A | | IL 1993-105221 | 19930330 |
| RU 2136656 | C1 | | WO 1993-US1991 | 19930305 |
| | | | RU 1994-45291 | 19930305 |
| AU 724115 | B | Div ex | AU 1997-33229 | 19970808 |
| | | | AU 1999-36759 | 19990624 |
| RO 115872 | B1 | | WO 1993-US1991 | 19930305 |
| | | | RO 1994-1601 | 19930305 |
| EP 633776 | B1 | | EP 1993-907233 | 19930305 |
| | | | WO 1993-US1991 | 19930305 |
| | | Related to | EP 1998-204466 | 19930305 |
| DE 69330206 | E | | DE 1993-630206 | 19930305 |
| | | | EP 1993-907233 | 19930305 |
| | | | WO 1993-US1991 | 19930305 |
| ES 2157923 | T3 | | EP 1993-907233 | 19930305 |
| PH 31379 | A | | PH 1993-45956 | 19930329 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9337910 | A | Based on | WO 9319749 |
| EP 633776 | A1 | Based on | WO 9319749 |
| JP 07508508 | W | Based on | WO 9319749 |
| US 5552438 | A | Based on | WO 9319749 |
| NZ 251092 | A | Based on | WO 9319749 |
| US 5614540 | A | Cont of | US 5552438 |
| AU 677776 | B | Previous Publ. | AU 9337910 |
| | | Based on | WO 9319749 |
| HU 70523 | T | Based on | WO 9319749 |
| US 5643946 | A | Cont of | US 5552438 |
| CZ 283425 | B6 | Previous Publ. | CZ 9402397 |
| | | Based on | WO 9319749 |
| NO 303116 | B1 | Previous Publ. | NO 9403663 |
| JP 2873090 | B2 | Previous Publ. | JP 07508508 |
| | | Based on | WO 9319749 |
| EP 919544 | A1 | Div ex | EP 633776 |
| SK 279958 | B6 | Previous Publ. | SK 9401171 |
| AU 705566 | B | Div ex | AU 677776 |
| | | Previous Publ. | AU 9733229 |
| AU 9936759 | A | Div ex | AU 705566 |
| RU 2136656 | C1 | Based on | WO 9319749 |
| AU 724115 | B | Div ex | AU 705566 |
| | | Previous Publ. | AU 9936759 |
| RO 115872 | B1 | Based on | WO 9319749 |
| EP 633776 | B1 | Related to | EP 919544 |
| | | Based on | WO 9319749 |

DE 69330206 E Based on EP 633776
Based on WO 9319749
ES 2157923 T3 Based on EP 633776

PRIORITY APPLN. INFO: US 1992-968762 19921030; US 1992-862030 19920402; US 1994-313094 19940929; US 1995-457942 19950518; US 1995-443636 19950518 ; SG 1996-7903 19930305

AN 1993-336568 [42] WPIDS
CR 1997-131824 [12]
AB WO 9319749 A UPAB: 20020823
Phenyl derivs. of formula (I), and their salts, are new: R1 = (CR4R5)nCOO(CR4R5)mR6, (CR4R5)nCONR4(CR4R5)mR6, (CR4R5)nO(CR4R5)mR6, or (CR4R5)rR6, where all alkyl moieties are opt. substd. by halo; m = 0-2; n = 1-4; r = 1-6; R4, R5 = H or 1-2C alkyl; R6 = H, Me, OH, aryl or aryloxy(1-3C)alkyl (both opt. substd. by halo), indanyl, indenyl, 7-11C polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, furanyl, etc. 3-6C cycloalkyl, or 4-6C cycloalkyl contg. 1-2 unsatd. bonds, where all cycloalkyl and heterocyclic gps. are opt. substd. by 1-3 Me or one Et; X = YR2, halo, NO2, NR4R5, or formylamine; Y = O or S(O)m'; m' = 0-2; X2 = O or NR8; X3 = H or X; X4 = a gp. of formula (i) or (ii): X5 = H, R9, OR8, CN, COR8, COOR8, CONR8R8 or NR8R8; R2 = Me or Et, both opt. substd. by halo; s = 0-4; R3 = H, halo, 1-4C alkyl, CH2NHCOCONH2, halo-substd. 1-4C alkyl, CH=CR8'R8', cyclopropyl (opt. substd. by R8'), CN, OR8, CH2OR8, NR8R10, CH2NR8R10, C(Z')H, COOR8, CONR8R10, or C=CR8'; Z' = O, NR9, NOR8, NCN, C(CN)2, CR8CN, CR8NO2, CR8COOR8, CR8CONR8R8, C(CN)NO2, C(CN)COOR9, or C(CN)NR8R8; Z = CY'R14, COOR14, CY'NR10R14, C(NR10)NR10R14, CN, C(NOR8)R14, C(NCN)SR9, etc. Het = 5-tetrazolyl, 2-, 4- or 5-imidazolyl, 5-imidazolidinyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-thiazolyl etc. The dotted line represents an opt. bond. Y' = O or S; R7 = (CR4R5)qR12 or 1-6C alkyl (where R12 or 1-6C alkyl are opt. substd. by one or more by Me or Et (themselves opt. substd. by 1-3F), F, Cl, Br, NO2, NR10R11, COR8, etc.q = 0, 1 or 2; R12 = 3-7C cycloalkyl, 2-, 3- or 4-pyridyl, pyrimidyl, pyrazolyl, 1- or 2-imidazolyl, thiazolyl, etc.; R8 = H or R9; R8' = R8 or F; R9 = 1-4C alkyl, opt. substd. by 1-3F; R10 = OR8 or R11; R11 = H or 1-4C alkyl (opt. substd. by 1-3F); or NR10R11 = a 5-7 membered ring contg. at least one additional heteroatom selected from O, N or S; R13 = oxazolidinyl, ozazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl etc.; R14 = H or R7; or NR10R14 = a 5-7 membered ring contg. at least one additional heteroatom selected from O, N or S; (c) when n is 1 and m is 0, then R6 (in (CR4R5)nO(CR4R5)mR6) is not H; (d) when R12 is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1; and (e) when X2R1 is OCF2H or OCF3, X is F, OCF2H or OCF3, X3 is H, s is O, X5 is H, Z is COOR14 and R14 is 1-7C unsubstd. alkyl, then R3 is not H.

USE/ADVANTAGE - (I) are useful as inhibitors of phosphodiesterase IV and are useful in treatment of allergic and inflammatory diseases such as asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis etc. (I) are also TNF inhibitors and thus useful in treatment of viral infections such as those caused by HIV-1, HIV-2, HIV-3, cytomegalovirus, adenovirus, influenza or **Herpes**, and animal viruses such as equine infectious anaemia virus, caprine arthritis virus, visna virus, maedi virus and other lentivirus. (I) may also be used to treat yeast and fungal infections, e.g., fungal meningitis. They may also be used to inhibit and/or reduce the toxicity of antifungal, antiviral and antibacterial agents.
Dwg.0/0

ABEQ US 5552438 A UPAB: 19961011
A compound of Formula (I), wherein: R1 is (CR4R5)nC(O)O(CR4R5)mR6, (CR4R5)nC(O)NR4(CR4R5)mR6, (CR4R5)nO(CR4R5)mR6, or (CR4R5)rR6; m is 0 to 2; n is 1 to 4; r is 0 to 6; R4 and R5 are hydrogen or a C1-2 alkyl; R6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxy C 1-3 alkyl, halo substituted aryloxy C1-3 alkyl, indanyl, indenyl, C7-11 polycycloalkyl; X is YR2, halogen, nitro, NR4R5, or formyl amine; Y is O or S(O)m'; m' is 0-2; X2 is O or NR8; X3 is hydrogen or X; X4 is (a) or (b); X5 is H, R9, OR8, CN, C(O)R8, C(O)OR8, C(O)NR8R8, or NR8R8; R2 is CH3 and -CH2CH3; s is 0 to 4; R3 is CN; Z' is O, NR9, NOR8, NCN, C(-CN)2, C(-CN)NO2, C(-CN)C(O)OR9, or C(-CN)C(O)NR8R8; Z is C(Y')R14, C(O)OR14, C(Y')NR10R14, C(NR10)NR10R14, CN, C(NOR8)R14, C(NCN)NR10R14, C(NCN)SR9, (2-,4- or 5-imidazolyl), (3-,4- or 5-pyrazolyl), (4- or 5-triazolyl (1,2,3)), (3- or 5-triazolyl(1,2,4)), (5-tetrazolyl), (2-,4- or 5-oxazolyl), (3-,4- or 5-isoxazolyl), (3- or 5-**oxadiazolyl** (1,2,4)); the dotted line in formula (a) represents a single or double bond; Y' is O or S; R7 is -(CR4R5)qR12 or C1-6 alkyl wherein the R12 or C1-6 alkyl group is optionally substituted by C1-2 alkyl, -F, -Br, -Cl, NO2, -NR10R11, -C(O)R8, -C(O)OR8, -OR8, -CN, -C(O)NR10R11, -OC(O)NR10R11, -OC(O)R8, -NR10C(O)NR10R11, -NR10C(O)C(O)NR10R11, -NR10C(O)C(O)R10, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl; q is 0-2; R12 is C3-C7-cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naphthyl, or phenyl; R8 is hydrogen or R9; R8, is R8 or fluorine; R9 is C1-4 alkyl; R10 is OR8 or R11; R11 is hydrogen, or C1-4 alkyl optionally substituted by one to three fluorines; R13 is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, **oxadiazolyl** , or thiadiazolyl, and each of these heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C1-2 alkyl groups; R14 is hydrogen; or the pharmaceutically acceptable salts thereof.
Dwg.0/0

ABEQ US 5614540 A UPAB: 19970516
Phenyl derivs. of formula (I), and their salts, are new: R1 = (CR4R5)nCOO(CR4R5)mR6, (CR4R5)nCONR4(CR4R5)mR6, (CR4R5)nO(CR4R5)mR6, or (CR4R5)rR6, where all alkyl moieties are opt. substd. by halo; m = 0-2; n = 1-4; r = 1-6; R4, R5 = H or 1-2C alkyl; R6 = H, Me, OH, aryl or aryloxy(1-3C)alkyl (both opt. substd. by halo), indanyl, indenyl, 7-11C polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, furanyl, etc. 3-6C cycloalkyl, or 4-6C cycloalkyl contg. 1-2 unsatd. bonds, where all cycloalkyl and heterocyclic gps. are opt. substd. by 1-3 Me or one Et; X = YR2, halo, NO2, NR4R5, or formylamine; Y = O or S(O)m'; m' = 0-2; X2 = O or NR8; X3 = H or X; X4 = a gp. of formula (i) or (ii): X5 = H, R9, OR8, CN, COR8, COOR8, CONR8R8 or NR8R8; R2 = Me or Et, both opt. substd. by halo; s = 0-4; R3 = H, halo, 1-4C alkyl, CH2NHCOCONH2, halo-substd. 1-4C alkyl, CH=CR8'R8', cyclopropyl (opt. substd. by R8'), CN, OR8, CH2OR8, NR8R10, CH2NR8R10, C(Z')H, COOR8, CONR8R10, or C=CR8'; Z' = O, NR9, NOR8, NCN, C(CN)2, CR8CN, CR8NO2, CR8COOR8, CR8CONR8R8, C(CN)NO2, C(CN)COOR9, or C(CN)NR8R8; Z = CY'R14, COOR14, CY'NR10R14, C(NR10)NR10R14, CN, C(NOR8)R14, C(NCN)SR9, etc. Het = 5-tetrazolyl, 2-, 4- or 5-imidazolyl, 5-imidazolidinyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-thiazolyl etc. The dotted line represents an opt. bond. Y' = O or S; R7 = (CR4R5)qR12 or 1-6C alkyl (where R12 or 1-6C alkyl are opt. substd. by one or more by Me or Et (themselves opt. substd. by 1-3F), F, Cl, Br, NO2, NR10R11, COR8, etc.q = 0, 1 or 2; R12 = 3-7C cycloalkyl, 2-, 3- or 4-pyridyl, pyrimidyl, pyrazolyl, 1- or 2-imidazolyl, thiazolyl, etc.; R8 = H or R9; R8' = R8 or

F; R9 = 1-4C alkyl, opt. substd. by 1-3F; R10 = OR8 or R11; R11 = H or 1-4C alkyl (opt. substd. by 1-3F); or NR10R11 = a 5-7 membered ring contg. at least one additional heteroatom selected from O, N or S; R13 = oxazolidinyl, ozazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl etc.; R14 = H or R7; or NR10R14 = a 5-7 membered ring contg. at least one additional heteroatom selected from O, N or S; (c) when n is 1 and m is 0, then R6 (in (CR4R5)nO(CR4R5)mR6) is not H; (d) when R12 is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1; and (e) when X2R1 is OCF2H or OCF3, X is F, OCF2H or OCF3, X3 is H, s is O, X5 is H, Z is COOR14 and R14 is 1-7C unsubstd. alkyl, then R3 is not H.

USE/ADVANTAGE - (I) are useful as inhibitors of phosphodiesterase IV and are useful in treatment of allergic and inflammatory diseases such as asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis etc. (I) are also TNF inhibitors and thus useful in treatment of viral infections such as those caused by HIV-1, HIV-2, HIV-3, cytomegalovirus, adenovirus, influenza or **Herpes**, and animal viruses such as equine infectious anaemia virus, caprine arthritis virus, visna virus, maedi virus and other lentivirus. (I) may also be used to treat yeast and fungal infections, e.g., fungal meningitis. They may also be used to inhibit and/or reduce the toxicity of antifungal, antiviral and antibacterial agents.

ABEQ US 5643946 A UPAB: 19970806

A cpd. of formula (I) and its salt is new:

R1 = e.g -(CR4R5)nC(O)O(CR4R5)mR6;

m = 0-2;

n = 1-4;

r = 0-6;

R4,R5 = H or a 1-2C alkyl;

R6 = H, methyl, hydroxyl, aryl, halo substituted aryl, aryloxy 1-3C alkyl,etc.;

provided that:

e.g. (a) when R6 is hydroxyl, then m is 2;

X = YR2, halogen, nitro, NR4R5, or formyl amine;

Y = O or S(O)m';

m' = 0-2;

X2 = O or NR8;

X3 = H or X;

X4 = a gp. of formula (a) or (b):

X5 = H, R9, OR8, CN, C(O)R8, C(O)OR8, C(O)NR8R8, or NR8R8;

R2 = -CH3 and -CH2CH3 optionally substituted by 1 or more halogens;

s = 0-4;

R3 = cyclopropyl optionally substituted by R8';

Z = C(Y')R14, C(O)OR14, C(Y')NR10R14,etc.;

the dotted line in formula (a) represents a single or double bond;

Y' = O or S;

R7 = e.g. -(CR4R5)qR12;

q = 0-2;

R12 = e.g. 3-7C-cycloalkyl;

R8 = H or R9;

R8' = R8 or fluorine;

R9 = 1-4C alkyl optionally substituted by one to three fluorines;

R10 = OR8 or R11;

R11 = H or 1-4C alkyl optionally substituted by one to three fluorines; or when R10 and R11 are as NR10R11 they may together with the nitrogen form a 5-7 membered ring optionally containing at least one additional heteroatom selected from O/N/or S;

R13 = e.g. oxazolidinyl;
R14 = H or R7; or when R10 and R14 are as NR10R14 they may together with the nitrogen form a 5 to 7 membered ring optionally containing one or more additional heteroatoms selected from O, N, or S;
provided that:
e.g. when R12 is e.g. N-pyrazolyl then q is not 1.
Dwg.0/0

L17 ANSWER 21 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1993-336567 [42] WPIDS
CROSS REFERENCE: 1993-386067 [48]; 1996-009476 [01]; 1997-288607 [26]
DOC. NO. CPI: C1993-148849
TITLE: New cyclohexane-ylidene derivs. - useful for inhibiting prodn. of tumour necrosis factor and treating allergic and inflammatory diseases.
DERWENT CLASS: B03 B05
INVENTOR(S): BENDER, P E; CHRISTENSEN, S B; FORSTER, C J; CHRISTENSEN, I S B
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 43
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9319748 | A1 | 19931014 | (199342)* | EN | 28 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE | | | | | |
| W: AT AU BB BG BR CA CH CZ DE DK ES FI GB HU JP KP KR LK LU MG MN MW NL NO NZ PL RO RU SD SE SK US | | | | | |
| AU 9337383 | A | 19931108 | (199408) | | |
| AU 9338079 | A | 19931108 | (199408) | | |
| ZA 9302261 | A | 19941130 | (199502) | | 56 |
| EP 633775 | A1 | 19950118 | (199507) | EN | |
| R: BE CH DE FR GB IT LI NL | | | | | |
| EP 636025 | A1 | 19950201 | (199509) | EN | |
| R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE | | | | | |
| JP 07508262 | W | 19950914 | (199545) | | 11 |
| EP 633775 | A4 | 19950222 | (199611) | | |
| EP 636025 | A4 | 19950222 | (199611) | | |
| CN 1092407 | A | 19940921 | (199716) | | |
| AU 708544 | B | 19990805 | (199943) | | |
| EP 633775 | B1 | 20000531 | (200031) | EN | |
| R: BE CH DE FR GB IT LI NL | | | | | |
| DE 69328778 | E | 20000706 | (200039) | | |
| EP 636025 | B1 | 20010718 | (200142) | EN | |
| R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE | | | | | |
| JP 3195353 | B2 | 20010806 | (200147) | | 13 |
| DE 69330459 | E | 20010823 | (200156) | | |
| ES 2158860 | T3 | 20010916 | (200164) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9319748 | A1 | WO 1993-US1990 | 19930305 |
| AU 9337383 | A | AU 1993-37383 | 19930305 |
| AU 9338079 | A | AU 1993-38079 | 19930312 |
| ZA 9302261 | A | ZA 1993-2261 | 19930330 |
| EP 633775 | A1 | EP 1993-906297 | 19930305 |

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|---|---|---|---|---|
| | | | WO 1993-US1990 | 19930305 |
| EP 636025 | A1 | | EP 1993-907493 | 19930312 |
| | | | WO 1993-US2325 | 19930312 |
| JP 07508262 | W | | JP 1993-517445 | 19930305 |
| | | | WO 1993-US1990 | 19930305 |
| EP 633775 | A4 | | EP 1993-906297 | |
| EP 636025 | A4 | | EP 1993-907493 | |
| CN 1092407 | A | | CN 1993-105726 | 19930402 |
| AU 708544 | B | Div ex | AU 1993-38079 | 19930312 |
| | | | AU 1996-71999 | 19961126 |
| EP 633775 | B1 | | EP 1993-906297 | 19930305 |
| | | | WO 1993-US1990 | 19930305 |
| DE 69328778 | E | | DE 1993-628778 | 19930305 |
| | | | EP 1993-906297 | 19930305 |
| | | | WO 1993-US1990 | 19930305 |
| EP 636025 | B1 | | EP 1993-907493 | 19930312 |
| | | | WO 1993-US2325 | 19930312 |
| JP 3195353 | B2 | | JP 1993-517445 | 19930305 |
| | | | WO 1993-US1990 | 19930305 |
| DE 69330459 | E | | DE 1993-630459 | 19930312 |
| | | | EP 1993-907493 | 19930312 |
| | | | WO 1993-US2325 | 19930312 |
| ES 2158860 | T3 | | EP 1993-907493 | 19930312 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9337383 | A | Based on | WO 9319748 |
| AU 9338079 | A | Based on | WO 9319750 |
| EP 633775 | A1 | Based on | WO 9319748 |
| EP 636025 | A1 | Based on | WO 9319750 |
| JP 07508262 | W | Based on | WO 9319748 |
| AU 708544 | B | Div ex | AU 675640 |
| | | Previous Publ. | AU 9671999 |
| EP 633775 | B1 | Based on | WO 9319748 |
| DE 69328778 | E | Based on | EP 633775 |
| | | Based on | WO 9319748 |
| EP 636025 | B1 | Based on | WO 9319750 |
| JP 3195353 | B2 | Previous Publ. | JP 07508262 |
| | | Based on | WO 9319748 |
| DE 69330459 | E | Based on | EP 636025 |
| | | Based on | WO 9319750 |
| ES 2158860 | T3 | Based on | EP 636025 |

PRIORITY APPLN. INFO: US 1992-968753 19921030; US 1992-862083 19920402; WO 1993-US2045 19930305

AN 1993-336567 [42] WPIDS

CR 1993-386067 [48]; 1996-009476 [01]; 1997-288607 [26]

AB WO 9319748 A UPAB: 20011105

Cyclohexane-ylidene derivs. of formula (I), and their pharmaceutically acceptable salts, are new. R1 = -(CR4R5)nC(O)O((CR4R5)mR6, -(CR4R5)nC(O)NR4(CR4R5)mR6, -(CR4R5)nO(CR4R5)mR6 or -(CR4R5)rR6; where alkyl moieties are opt. substd. with 1 or more halogen; m = 0-2; n = 1-4; r = 1-6; R4, R5 = H or 1-2C alkyl; R6 = H, Me, OH, aryl, opt. halo-substd., aryloxy (1-3C) alkyl) opt. halo-substd., indanyl, indenyl, 7-11C polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl,

3-6C cycloalkyl or 4-6C cycloalkyl contg. 1 or 2 unsatd. bonds, where cycloalkyl and heterocyclic moieties are opt. substd. with 1-3 Me or one Et; provided that: a) when R6=OH, then m = 2; or b) when R6 = OH, then r = 2-6; or c) when R6 = 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m = 1 or 2; or d) when R6 = as for (c), then r = 1-6; e) when n = 1 and m = 0, then R6 is other than H in -(CR4R5)nO(CR4R5)mR6; X = YR2, halogen, NO2, NR4R5 or formyl amine; Y = O or S(O)m'; m' = 0-2; X2 = O or NR8; X3 = H or X; R2 = Me or Et opt. substd. by 1 or more halogen; s = 0-4; R3 = H, halogen, 1-4C alkyl opt. halo-substd., CH2NHC(O)C(O)NH2, -CH=CR8'R8', cyclopropyl opt. substd. by R8', CN, OR8, CH2OR8, NR8R10, CH2NR8R10, C(Z')H, C(O)OR8, C(O)NR8R10 or C=CR8'; Z' = O, NR9, NOR8, NCN, C(-CN)2, CR8CN, CR8NO2, CR8C(O)OR8, CR8C(O)NR8R8, C(-CN)NO2, C(-CN)C(O)OR9 or C(-CN)C(O)NR8R8; Z = C(-CN)2, CR14CN, CR14C(O)OR8, CR14C(O)NR8R14, C(-CN)NO2, C(-CN)C(O)OR9, C(-CN)OC(O)R9, C(-CN)OR9 or C(-CN(C(O)NR8R14; R7 = -(CR4R5)qR12 or 1-6C alkyl (where R12 and alkyl are opt. substd. by 1 or more Me or Et opt. substd. by 1-3 F), F, Br, Cl, NO2, -NR10R11, -C(O)R8, -CO2R8, -OR8, -CN, -C(O)NR10R11, -OC(O)NR10R11, -OC(O)R8, -NR10C(O)NR10R11, -NR10C(O)R11, -NR10C(O)OR9, -NR10C(O)R13, -C(NR10)NR10R11, -C(NCN)NR10R11, -C(NCN)SR9, -NR10C(NCN)SR9, -NR10C(NCN)NR10R11, -NR10S(O)2R9, -S(O)m'R9, -NR10C(O)C(O)NR10R11, -NR10C(O)C(O)R10,, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl or tetrazolyl; q = 0-2; R12 = 3-7C cycloalkyl; 2-, 3- or 4-pyridyl; pyrimidyl, pyrazolyl; 1- or 2-imidazolyl; thiazolyl; triazolyl; pyrrolyl, piperazinyl; piperidinyl,; morpholinyl; furanyl; 2- or 3-thienyl; 4- or 5-thiazolyl; quinolinyl; naphthyl; or Ph; R8 = H or R9; R8' = R8 or F; R9 = 1-4C alkyl opt. substd. by 1-3F; R10 = OR8 or R11; R11 = H or 1-4C alkyl opt. substd. by 1-3 F; or when R10 and R11 are NR10R11, they may together with N form a 5-7 membered ring opt. contg. at least one additional O, N or S; R13 = oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, **oxadiazolyl**, or thiadiazolyl, and each heterocyclic ring is connected through a C, and is opt. substd. by 1 or 2 1-2C alkyl; R14 = H or R7; or when R8 and R14 are as NR8R14 they may together with N forma 5-7 membered ring opt. contg. 1 or more additional O, N or S; provided that when R12 is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl or N-morpholinyl, then q is not 1.

USE - (I) inhibit cyclic nucleotide phosphodiesterase IV or the prodn. of Tumour Necrosis Factor nd are useful for treating allergic and inflammatory diseases (claimed) e.g. asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic or vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome, also diabetes insipidus and CNS disorders. (I) can also be used to treat viruses HIV-1,2 and 3, cytomegalovirus, influenza, adenovirus and **Herpes** viruses; also yeast and fungal infections, e.g. funal meningitis. (I) may also be used for inhibiting and/or reducing toxicity of anti-fungal, anti-bacterial or anti-viral agents e.g. Amphotericin B. Daily oral dosage is 0.001-100, pref. 0.01-40 mg/kg, in 1-6 doses.

Dwg.0/0

L17 ANSWER 22 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1993-336566 [42] WPIDS
DOC. NO. CPI: C1993-148848
TITLE: New phenyl-cyclohexane cpds. - useful as phosphodiesterase IV and tumour necrosis factor

inhibitors.
DERWENT CLASS: B03 B05 C02 C03
INVENTOR(S): CHRISTENSEN, S B; CHRISTENSEN, I S B
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 42
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9319747 | A1 | 19931014 | (199342)* | EN | 30 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE | | | | | |
| W: AT AU BB BG BR CA CH CZ DE DK ES FI GB HU JP KP KR LK LU MG MN MW NL NO NZ PL RO RU SD SE SK US | | | | | |
| AU 9337382 | A | 19931108 | (199408) | | |
| EP 634930 | A1 | 19950125 | (199508) | EN | |
| R: BE CH DE FR GB IT LI NL | | | | | |
| CN 1094711 | A | 19941109 | (199544) | | |
| JP 07508261 | W | 19950914 | (199545) | | 12 |
| EP 634930 | A4 | 19950222 | (199611) | | |
| US 5602173 | A | 19970211 | (199712) | | 12 |
| JP 3195352 | B2 | 20010806 | (200147) | | 14 |

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| WO 9319747 | A1 | | WO 1993-US1988 | 19930305 |
| AU 9337382 | A | | AU 1993-37382 | 19930305 |
| EP 634930 | A1 | | EP 1993-906296 | 19930305 |
| | | | WO 1993-US1988 | 19930305 |
| CN 1094711 | A | | CN 1993-105721 | 19930402 |
| JP 07508261 | W | | JP 1993-517444 | 19930305 |
| | | | WO 1993-US1988 | 19930305 |
| EP 634930 | A4 | | EP 1993-906296 | |
| US 5602173 | A | CIP of | US 1992-862112 | 19920402 |
| | | CIP of | US 1992-968760 | 19921030 |
| | | | WO 1993-US1988 | 19930305 |
| | | | US 1994-313096 | 19940929 |
| JP 3195352 | B2 | | JP 1993-517444 | 19930305 |
| | | | WO 1993-US1988 | 19930305 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9337382 | A | Based on | WO 9319747 |
| EP 634930 | A1 | Based on | WO 9319747 |
| JP 07508261 | W | Based on | WO 9319747 |
| US 5602173 | A | Based on | WO 9319747 |
| JP 3195352 | B2 | Previous Publ. | JP 07508261 |
| | | Based on | WO 9319747 |

PRIORITY APPLN. INFO: US 1992-968760 19921030; US 1992-862112 19920402; US 1994-313096 19940929
AN 1993-336566 [42] WPIDS
AB WO 9319747 A UPAB: 19931202
Cyclohexyl-phenyl derivs. of formula (I), and their salts, are new. In (I) R1 is (CR4R5)nC(O)O(CR4R5)mR6, (CR4R5)nC(O)NR4(CR4R5)mR6,

(CR4R5)nO(CR4R5)mR6, or (CR4R5)rR6, where all alkyl moieties are opt. substd. by halo; m is 0-2; n is 1-4; r is 1-6; R4, R5 are H or 1-2C alkyl; R6 is H, Me, OH, aryl or aryloxy(1-3C)alkyl (both opt. substd. by halo), indanyl, indenyl, 7-11C polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, 3-6C cycloalkyl, or 4-6C cycloalkyl contg. 1-2 unsatd. bonds, where all cycloalkyl and heterocyclic gps. are opt. substd. by 1-3 Me, or one Et; X is YR2, halo, NO2, NR4R5, or formylamine; Y is O or S(O)m'; m' is 0-2; X2 is O or NR8; X3 is H or X; R2 is Me or Et, both opt. substd. by halo; s is 0-4; R3 is H, halo, 1-4C alkyl, CH2NHCOCONH2, etc.

USE/ADVANTAGE - (I) are useful as inhibitors of phosphodiesterase IV and thus useful in treatment of allergic and inflammatory diseases such as asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, adult respiratory distress syndrome, and in treatment of diabetes insipidus and CNS disorders such as depression and multi-infarct dementia. (I) are also TNF inhibitors and thus useful in treatment of viral infections such as those caused by HIV-1, HIV-2, HIV-3, cytomegalovirus, adenovirus, influenza or **Herpes**, and animal viruses such as equine infectious anaemia virus, caprine arthritis virus, visna virusm maedi virus and other lentivirus. (I) may also be used to treat yeast and fungal infections, e.g., fungal menigitis. They may also be used to inhibit and/or reduced the toxicity of antifungal, antiviral and antibacterial agents.

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ABEQ US 5602173 A UPAB: 19970320

A cpd. of formula (I) or its salts: R1 = -(CR4R5)nC(O)O(CR4R5)mR6, -(CR4R5)nC(O)NR4(CR4R5)mR6,-(CR4R5)nO(CR4R5)mR6, or -(CR4R5)rR6; the alkyl moieties may be opt. substd. by one or more halo; m = 0 to 2; n = 1 to 4; r = 0 to 6; R4, R5 = H or 1-2C alkyl; R6 = H, methyl, hydroxy, aryl, halo substd. aryl, aryloxy 1-13C alkyl, halo substd. aryloxy 1-13C alkyl, indenyl, indenyl, 7-11C polycycloalkyl 3-6C cycloalkyl, or a 4-6C cycloalkyl contg. one or two unsatd. bonds, the cycloalkyl moiety may be opt. substd. by 1 to 3 methyl or one ethyl; provided that: a) when R6 = hydroxy, then m = 2; or b) when R6 = hydroxy, then r = 2 to 6; or c) when n = 1 and m = 0, then R6 is not H in -(CR4R5)nO(CR4R5)mR6; X = YR2, halo, nitro, NR4R5, or formyl amine; Y = O; m' = 0 - 2 ; X2 = O or NR8; X3 = hydrogen or X; R2 = -CH3 or -CH2CH3 opt. substd. by 1 or more halo; s = 0 - 4; R3 = CN; Z = CR8R8OR14, CR8R8OR15, CR8R8SR14, CR8R8SR15, CR8R8S(O)m'R7, CR8R8NR10R14, CR8R8NR10S(O)2NR10R14, CR8R8NR10S(O)2R7, CR8NR10C(Y')R14, CR8R8NR10C(O)OR7, CR8R8NR10C(Y')NR10R14, CR8R8NR10C(NCN)NR10R14, CR8R8NR10C(CR4NO2)NR10R14, CR8R8NR10C(NCN)SR9, CR8R8NR10C(CR4NO2)SR9, CR8R8C(O)OR14, CR8R8C(Y')NR10R14, CR8R8C(NR10)NR10R14, CR8R8CN, CR8R8(tetrazolyl), CR8R8(imidazolyl), CR8R8(imidazolidinyl), CR8R8(pyrazolyl), CR8R8(thiazolyl), CR8R8(thiazolidinyl), CR8R8(oxazolyl), CR8R8(oxazolidinyl), CR8R8(triazolyl), CR8R8(isoxazolyl), CR8R8(**oxadiazolyl**), CR8R8(thiadiazolyl), CR8R8(morpholinyl), CR8R8(piperidinyl), CR8R8(piperazinyl), CR8R8(pyrrolyl), CR8R8C(NOR8)R14, CR8R8C(NOR14)R8, CR8R8NR10C(NR10)SR9, CR8R8NR10C(NR10)NR10R14, CR8R8NR10C(O)C(O)NR10R14, or CR8R8NR10C(O)C(O)OR14; Y' = O; R7 = -(CR4R5)qR12 or 1-6C alkyl; R12 or 1-6C alkyl is opt. substd. by one or more 1-2C alkyl opt. substd. by 1-3 -F, -Br, -Cl, -NO2, -NR10R11, -C(O)R8, -C(O)OR8, -OR8, -CN, -C(O)NR10R11, -OC(O)NR10R11, -OC(O)R8, -NR10C(O)NR10R11, -NR10C(O)R11, -NR10C(O)OR9, -C(NR10)NR10R11, -C(NCN)NR10R11, -C(NCN)SR9, -NR10C(NCN)SR9,

-NR10C(NCN)NR10R11, -NR10S(O)2R9, -S(O)m'R9, -NR10C(O)C(O)NR10R11 or NR10C(O)C(O)R10; q = 0 - 2; R12 = 3-7C cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naphthyl, or phenyl; R8 = H or R9; R8' = R8 or fluorine; R9 = 1-4C alkyl opt. substd. by 1-3 F; R10 = OR8 or R11; R11 = H, or 1-4C alkyl opt. substd. by 1-3 F; or NR10R11 = 5 to 7 membered ring opt. contg. at least one additional O, N, or S; R14 = H or R7; R15 = C(O)R14, C(O)NR4R14, S(O)2R7, or S(O)2NR4R14.
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L17 ANSWER 23 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1993-134358 [16] WPIDS
DOC. NO. CPI: C1993-059968
TITLE: New pyrrolidinone(s) - inhibit TNF and phosphodiesterase IV in the prodn. treatment of allergies, inflammatory diseases etc..
DERWENT CLASS: B03
INVENTOR(S): BENDER, P E; CHRISTENSEN, S B; CHRISTENSEN, S B
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
COUNTRY COUNT: 22
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9307141 | A1 | 19930415 | (199316)* | EN | 44 |
| RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL SE | | | | | |
| W: AU CA JP KR US | | | | | |
| AU 9228690 | A | 19930503 | (199334) | | |
| ZA 9207787 | A | 19930825 | (199339) | | |
| PT 100947 | A | 19940228 | (199412) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9307141 | A1 | WO 1992-US8611 | 19921002 |
| AU 9228690 | A | AU 1992-28690 | 19921002 |
| ZA 9207787 | A | ZA 1992-7787 | 19921009 |
| PT 100947 | A | PT 1992-100947 | 19920904 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9228690 | A | Based on | WO 9307141 |

PRIORITY APPLN. INFO: US 1992-916733 19920720; US 1991-776508 19911011; US 1992-916713 19920720
AN 1993-134358 [16] WPIDS
AB WO 9307141 A UPAB: 19950626
Heterocyclic-3-phenylpyrrolidin-2-one derivs. of formula (I) and their salts are new. In the formula R1 = e.g. 1-12C alkyl (opt. substd. by halo), 3-6C cycloalkyl (opt. substd. by 1-3 Me or Et), 4-6C cycloalkenyl, 7-11C polycycloalkyl, etc.; X1 = O or S; X2 = O or NR14; X3 = H or X; X = YR2, halo, NO2, NR14R14 or formamide; Y = O or S(O)m; R2 = Me or Et opt. substd. by F; R3 = e.g. H, halo, CN, 1-4C alkyl (opt. substd. by halo), cyclopropyl (opt. substd.) etc.; R3' = e.g. H, halo, 1-4C alkyl (opt. halo

substd.), cyclopropyl (opt. substd.), etc.; A = 2-, 3-, or 4-pyridinyl, 4-morpholinyl or piperidinyl, 1-, 2-, 4-, or 5-imidazolyl, 2- or 3-thienyl, 2- or 5-pyrimidyl or 4- or 5-thiazolyl (all opt. substd.); R8 = H, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-pyrazolyl, 4- or 5-triazolyl-(1,2,3), 3- or 5-(triazolyl(1,2,4), 5-tetrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 3- or 5-**oxadiazolyl**(1,2,4), 2-**oxadiazolyl**(1,3,4), 2-thiadiazolyl(1,3,4), 2-, 4- or 5-thiazolyl, 2-, 4- or 5-thiazolidinyl or 2-, 4- or 5-imidazolidinyl, etc. (all opt. ring substd.); R14 = H or 1-12C alkyl (opt. halo substd.); m = 0-2; q = 0-1.

USE/ADVANTAGE - (I) inhibit phosphodiesterase IV and TNF and are used to treat e.g. allergic, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. They also treat diabetes insipidus and CNS disorders such as depression and multiinfarct dementia. (I) also treat HIV (e.g. HIV-1, -2 and -3) ARC or any other disease associated with HIV infection. They treat viral infections such as cytomegalovirus, influenza, adenovirus and **herpes** viruses such as **Herpes** zoster and **Herpes** simplex. The cpds. also treat yeast and fungal infections e.g. fungal meningitis and candida infections. The cpds. may also inhibit and/or reduce the toxicity of antifungal, antibacterial or antiviral agents.

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ABEQ ZA 9207787 A UPAB: 19931123

Heterocyclic-3-phenylpyrrolidin-2-one derivs. of formula (I) and by halo), 3-6C cycloalkyl (opt. substd. by 1-3 Me or Et). 4-6C cycloalkenyl, 7-11C polycycloalkyl, etc.; X1 = O or S; X2 = O or NR14; X3 = H or X; X = YR2, halo, NO2, NR14R14 or formamide; Y = O or S(O)m; R2 = Me or Et opt. substd. by F; R3 = e.g. H, halo, CN, 1-4C alkyl (opt. substd. by halo), cyclopropyl (opt. substd.) etc.; R3' = e.g. H, halo, 1-4C alkyl (opt. halo substd.), cyclopropyl (opt. substd.), etc.; A = 2-, 3-, or 4-pyridinyl, 4-morphilinyl or piperidinyl, 1-, 2-, 4-, or 5-imidazolyl, 2- or 3-thienyl, 2- or 5-pyrimidyl or 4- or 5-thiazolyl (all opt. substd.); R8 = H, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-pyrazolyl, 4- or 5-triazolyl-(1,2,3), 3- or 5-(triazolyl(1,2,4), 5-tetrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 3- or 5-**oxadiazolyl**(1,2,4), 2-**oxadiazolyl**(1,3,4), 2-thiadiazolyl(1,3,4), 2-, 4- or 5-thiazolyl, 2-, 4- or 5-thiazolidinyl or 2-, 4- or 5-imidazolidinyl, etc. (all opt. ring substd.); R14 = H or 1-12C alkyl (opt. halo substd.); m = 0-2; q = 0-1.

USE/ADVANTAGE - (I) inhibits phosphodiesterase IV and tNF and are used to treat e.g. allergic, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, etc. They also treat diabetes insipidus and CNS disorders such as depression and multiinfarct dementia. (I) also treat HIV (e.g. HIV-1, -2 and -3) ARC or any other disease associated with HIV infection.